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ISLAND MEDICAL JOURNAL

October 1991

Volume 74, Number 10

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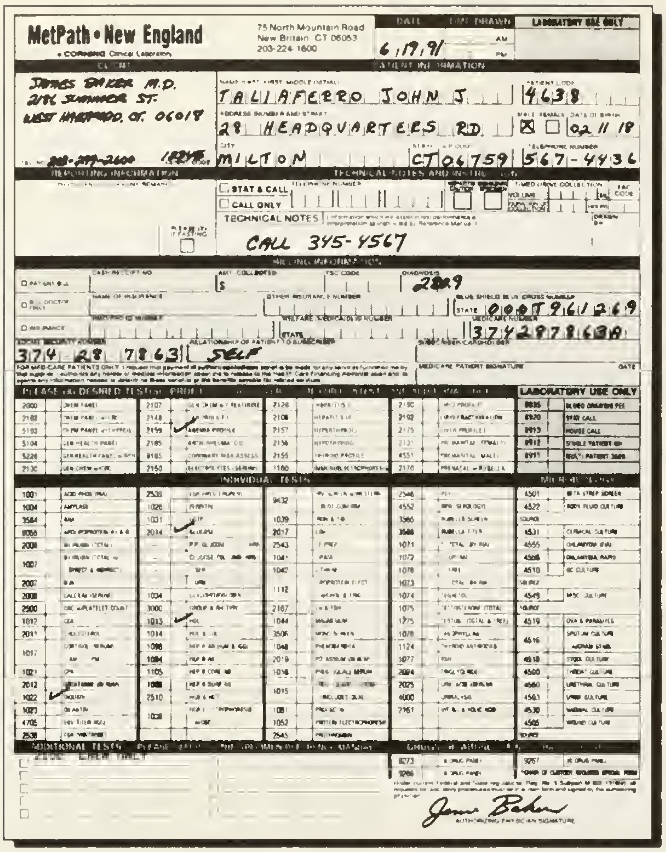

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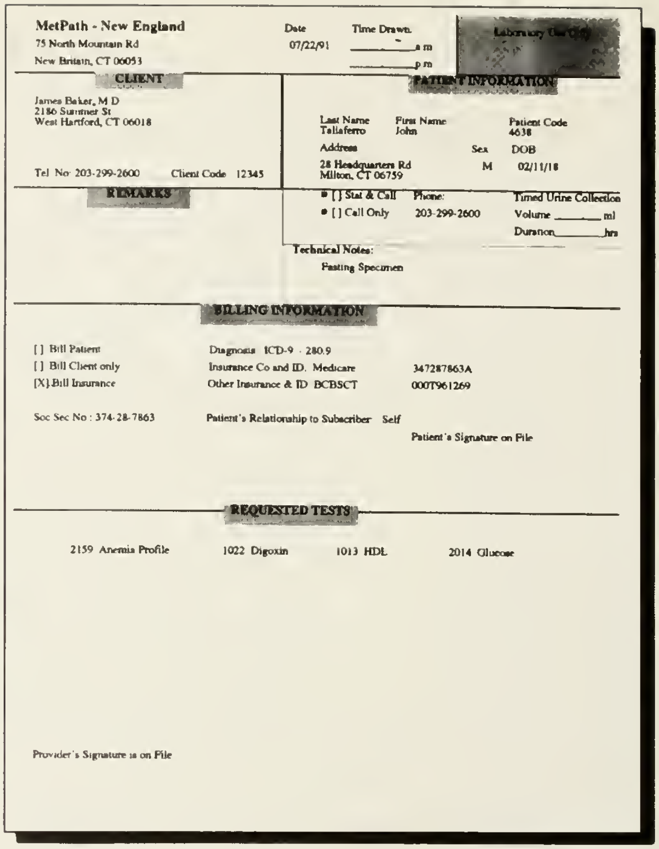

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Volume 74, Number 10 October 1991

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Cover: *The co-discoverers of insulin, Dr Charles Best and Sir Frederick Banting of the University of Toronto. At the time of the initial experiments, Best was still a medical student. In 1923, Banting and Professor John Macleod were awarded the Nobel Prize in Medicine for their contributions toward the action and usage of insulin. Courtesy of American Diabetes Association, RI Affiliate.*

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COMMENTARIES

Diabetes Mellitus

Before the isolation of insulin by Banting, Best and Macleod in 1922, diabetes mellitus had been held to be an extremely serious, frequently fatal, disease. A decade before their seminal discovery, a major text declared: "The complications of the disease are many and serious. It may cause impaired vision by weakening the muscles of accommodation, or by lessening the sensitiveness of the retina to light. Also cataract is very common. Skin affections of all kinds may occur and prove very intractable. Boils, carbuncles, cellulitis and gangrene are all apt to occur as life advances. Diabetics are especially liable to phthisis and pneumonia, and gangrene of the lung may set in if the patient survives the crisis. Diabetes is a very fatal form of disease, recovery being exceedingly rare." Indeed, prognostic surveys in the pre-insulin era showed that 63.8% died in diabetic coma.

The amazing advances achieved in the maintenance of the diabetic during the past 69 years should still the doubts of those who question the contributions of clinical research. But problems remain and further laboratory and bedside inquiry is needed. Two articles in this month's *Journal* indicate that diabetes mellitus remains a principal cause of blindness in developed nations of the world despite an effective treatment to prevent loss of vision. Here, the problem may rest in the domain of education and health care financing rather than in basic research. A third article explores the possible merits, and risks, of using a new form of insulin structurally akin to the human insulin molecule. The results are currently inconclusive and the authors indicate the pressing need for further clinical trials.

What was once held to be a fatal illness is now a manageable disorder. It was diligent investigation which brought us from the paralysis of despair to that point where a diabetic can live productively; and it will be further research which will allow us finally to abolish the many residual complications of diabetes.

The word insulin, incidentally, was coined in 1923 not by Banting and his colleagues but by the British physiologist, Sir Edward AW Sharpey, to describe the newly recognized hormone secreted by the pancreatic islands of Langerhans [L. *insula* - island plus the chemical suffix - in].

Stanley M. Aronson, MD

The Hippocratic Oath

A promise is a promise - but an oath is something substantially more. It represents a sworn compact typically invoking deities; and when unfulfilled, it carries the weight of sanctions or penalties.

The bargaining formula of an oath is simple: If I perform a particular act, then something (customarily out of my hands) will be given to me by the invoked powers. If, however, I fail to carry out this act, then a terrible fate awaits me.

No culture is without its oaths and accompanying rituals, often attended by various symbolic gestures of the hands. Abraham, in demanding an oath from one of his servants, asked that he place his hand under his master's thigh (Genesis 24:2; also 47:29). Roman custom required the placing of one's hands between the hands of those to whom the oath was directed. This rite persisted in the medieval act of fealty. During the last few centuries, placing one's hand upon the scriptural text of one's faith has become the mark for validating a sworn oath. Swearing upon the Gospels (*tactis sacrosanctis Evangeliis*) was uniformly observed throughout Europe until the Reformation and is still at the core of most oath-taking ceremonies. The procedure of lifting one's hand when taking an oath seems to originate in Hebrew custom (Genesis 14:24 and Deut. 32:40).

In Matthew 5:34 Jesus says, "But I say to you, Do not swear at all . . ." This has been interpreted by some sects, notably Quakers, Mennonites and Anabaptists, as a proscription against all oaths. Refusal by Quakers to take judicial oaths finally led to legislative easement in nineteenth century England. For those who even denied the contractual force of an oath (eg, atheists) or those believing it to be contrary to their faith (eg, Quakers), The Oaths Act of 1888 permitted them, rather, " . . . to make a solemn affirmation." Affirmation attests to a certain truth without resorting to divine authority.

The wording of most oaths, through the centuries, has tended to become increasingly stereotyped. Thus, the Charlemagnian phrase, "*Sic me adjuvet Deus*" persists to this day as, "So help me God." The root phrase of all Anglo-Scottish judicial oaths (" . . . shall be the truth, the whole truth, and nothing but the truth") has remained unchanged for over eight centuries.

Oaths spoken in anger or as an accompaniment to some frivolity have given an alternate meaning to the act of swearing. Indeed, unless further described, swearing is usually considered a wicked act. Such oaths are said to be uttered, symbolically, outside of the temple (L. *pro fanes*) and accordingly are labelled as deeds of profanity. In all cultures, the typical child has learned the earthy language of swearing before he has learned how to write.

Oaths of all varieties, sacred or profane, are pervasive in our society. No ordination, no judicial testimony, no inauguration into office, no entrance into the military or marriage is complete without its ritual oath. Indeed, the final sentence of the Declaration of Independence is a memorable oath pledging the lives, the fortunes and the sacred honors of its signatories.

Many professions, including medicine, have devised solemn oaths when introducing novitiates to the inner ranks of their discipline. Western physicians customarily take such an oath, called Hippocratic, minutes before the doctoral degree is granted to them. Generations of doctors have sworn to uphold the tenets of this pledge and it has become a virtually indispensable icon of western medicine. These are its words:

> *I swear by Apollo Physician, by Asclepius, by Health, by Panacea and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture. To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money to share mine with him; to consider his family as my own brothers, and to teach them this art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physicians oath, but to nobody else. I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrongdoing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course. Similarly I will not give a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art. I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as are craftsmen therein. Into whatsoever houses I enter, I will enter to help the sick, and I will abstain from all intentional wrongdoing and harm, especially from abusing the bodies of man or woman, bond or free. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets. Now if I carry out this oath, and break it not, I gain for ever reputation among all men for my life and for my art; but if I transgress it and forswear myself, may the opposite befall me.*

This is a majestic statement of professional ethic, with declarations not easily forgotten. Is there a physician who is not moved by its two most persuasive statements: "Into whatsoever houses I enter . . ." and "And whatsoever I shall see or hear . . . ."? But yet a sworn pledge is a sworn pledge and one must accept all parts of the oath not merely those parts which are at the moment acceptable. We cannot, for example, pledge to uphold the Constitution of the United States - ignoring those Amendments with which we currently disagree. An oath is an unqualified pledge not a bargaining session.

When the Hippocratic Oath is viewed some two and a half millennia after its creation, there are values within it which are enduring, some which are at best ambiguous, and some contrary to the current principles (and capabilities) of medicine. The Oath talks with conviction of the physician's responsibilities to his personal patient - but says nothing of a larger responsibility to the health of the public; nothing, too, about research, the advancement of knowledge or the sharing of such disclosures with all regardless of whether or not they are one's personal students. The Oath would appear to restrict the study of medicine to those males whose fathers are physicians. Monotheists might feel uneasy with its introductory sentence; and of course, surgeons, oncologists and gynecologists could not, with integrity, enter into such an Oath.

We have, then, choices: We may swear the unaltered Hippocratic Oath as an act of historic sentimentality, not believing many of its provisions (oaths are but words, said Butler, and words but wind). Alternatively, we may cease our use of the Oath, substituting a more appropriate one. Or, we may, with caution, elect to change some of its words while preserving its traditional stipulations.

The historic verities within the Oath are not to be denied. It recognizes, tacitly, that learning is an essential part of the art of medicine. Cannot, therefore, this important Oath be amended by the many things we have learned in the last few millennia such that a rewording could be sworn to without reservation?

The *Journal* has asked a number of Rhode Island practitioners to discuss the Hippocratic Oath and its applicability to medicine as we now approach the margins of the twenty-first century. We will publish these commentaries in a future issue.

Stanley M. Aronson, MD

The Language of Epidemiology (IV): Rate

Thomas Sydenham, England's leading clinician during the seventeenth century, could do no better than observe that small pox seemed to be considerably more common in 1673 than in the preceding few years. It did not occur to the leading clinician of his day to specify the annual numbers of verified cases in the region he was commenting about and state how many persons were at risk of contracting the disease in that region. His dilemma is similar to a physician observing that a patient was perhaps more feverish today than yesterday without providing any quantitative measure of the fever. A simple, quantitative expression by which the disease burden in one region might be compared with that in another region, or one year with another, had not yet been devised in the 17th century.

Such information is best expressed as an incidence rate. Within scientific discourse, the concept of rate seems so basic, so intuitive, that it comes as a surprise to learn that rates for purpose of comparison have been employed only in the last century.

A rate incorporates three separate, numeric variables: (1) the number of recorded happenings (eg, births, illnesses, deaths, etc), sometimes called the numerator value; (2) the number of people who are at risk for this happening (or incident) sometimes called the denominator value; and (3) the time interval during which these happenings had been enumerated. The number of vulnerable persons (ie, those in the denominator population who are at risk of entering the numerator population) may be combined with the time-interval of observation to produce a merged denominator called person-years which is a two-dimensional expression of vulnerability. Thus, for example, 24 people each exposed for six months to a disease-producing factor, or 36 persons each exposed for four months, or 12 persons each exposed for one year, will each equal 12 person-years. The exposure-agent might

TYPE OF RATE	NUMERATOR	DENOMINATOR	TIME INTERVAL
Incidence	number new cases*	living population**	one year
Mortality	number deaths*	living population	one year
Birth	number living births	living population	one year
Fertility	number living births	women, ages 15-44 yrs	one year
Infant Mortality	number deaths below one year	number live births	one year
Neonatal mortality	number deaths below age 28 days	number live births	one year
Attack	number new cases*	number at risk	epidemic interval
Case fatality	number dying*	number ill*	epidemic interval

---

* of a specific disease

** living population at mid interval; if, for example, the rate describes the mortality in Providence for the year 1934, the mid-year population is used as the denominator since it approximates most closely the population throughout the year.

be an industrial pollutant, a dietary factor, a life-style or proximity to a communicable pathogen.

A rate represents past observations, but is commonly used to predict future likelihoods (ie, probabilities). For example, if the 1975 incidence rate for colon cancer in Rhode Island was 33 per 100,000, it will form the standard of expectation for the succeeding few years. Operationally, the number of onsets can also be considered a measure of the velocity of conversion (ie, from health to sickness, from non-pregnancy to pregnancy, from life to death) essentially the movement from the denominator to the numerator population. Most conversions are unidirectional (eg, life to death) but some, such as pregnancy, are bidirectional.

What factors influence the accuracy of a rate? If our gathering, or ascertainment, of cases is less than complete, the rate will be lower than the true value; if, on the other hand, our estimate of the base (denominator) population is low, the rate will appear to be higher than the true value. Varying thresholds of diagnostic sensitivity will also alter the rates. If the incidence rate of tuberculosis in city A is determined solely by the number of clinically ill with positive sputa, while in city B (perhaps with more resources) X-ray screening is widely performed and the presence or absence of tuberculosis determined by radiographic changes, it is likely that the recorded infection rate in city B will seem higher than in city A, assuming that the two cities are otherwise similar.

There are many incidence rates which have become essential parts of medical thinking. A few of them are defined in the table on the previous page.

As an isolated bit of information, 62 is a pure number; when it describes something tangible (62 cases of typhoid) it becomes a statistic; however, a rate (62 cases of typhoid per 100,000 Rhode Island population for the year 1907) provides both quantitative and temporal dimension to the situation and permits us then to make insightful comparisons with other regions or with other times and offers a predictive framework for anticipating the immediate future.

Stanley M. Aronson, MD

Surveillance in the Time of Cholera

The seventh Western Hemispheric pandemic of cholera began in Peru on January 23, 1991. Within five months additional outbreaks of clinical cholera had been recorded in Colombia, Ecuador, Brazil, Chile, as well as a few isolated cases in the United States. The *Vibrio cholerae* 01 strains isolated from these affected countries were all serotype Naba, biotype El Tor, suggesting that the pandemic arose from a single source.

The table provides some details of this cholera pandemic affecting, conservatively estimated, over a quarter of a million persons.

The 14 identified cases in the United States are confined to the states of Georgia, Florida, New York and New Jersey. All 14 patients had either returned recently from Peru and Ecuador (2 patients), or had consumed shellfish recently brought in from Ecuador (12 patients). No secondary infections involving family or neighbors have yet been noted.

Travelers to South America, particularly to the Pacific tier countries, should be advised that the drinking water and the sewage services are frequently suboptimal. An estimated 88% of urban homes have access to piped drinking water, but only 55% of rural homes have a drinking water supply. In urban areas, 80% of the homes have sanitation coverage but only 32% of rural homes are connected to sewer systems. According to Pan American Health Organization, ""Most of the treatment plants produced water of poor bacteriological quality; only two of the 40 rural systems claiming to practice chlorination showed chlorine residuals." In samples taken from Peruvian urban areas, " . . . water samples were found to contain cholera organisms." Although on a per capita basis Latin America and the Caribbean nations enjoy the most

Country	1st Case	No. Cases*	No. Deaths	Attack Rate**	CFR#
Peru	1/23/91	223,564	2,163	1,037	1.0%
Ecuador	3/1/91	24,435	391	2259	1.6%
Colombia	3/30/91	2,599	31	8	1.2%
Chile	4/7/91	41	2	<1	4.9%
Brazil	4/22/91	18	0	<1	0%
USA	4/9/91	14	0	<1	0%
Mexico	6/17/91	27	0	<1	0%

*As of June, 1991

** Attack Rate = No. identified cases per 100,000 population at risk.

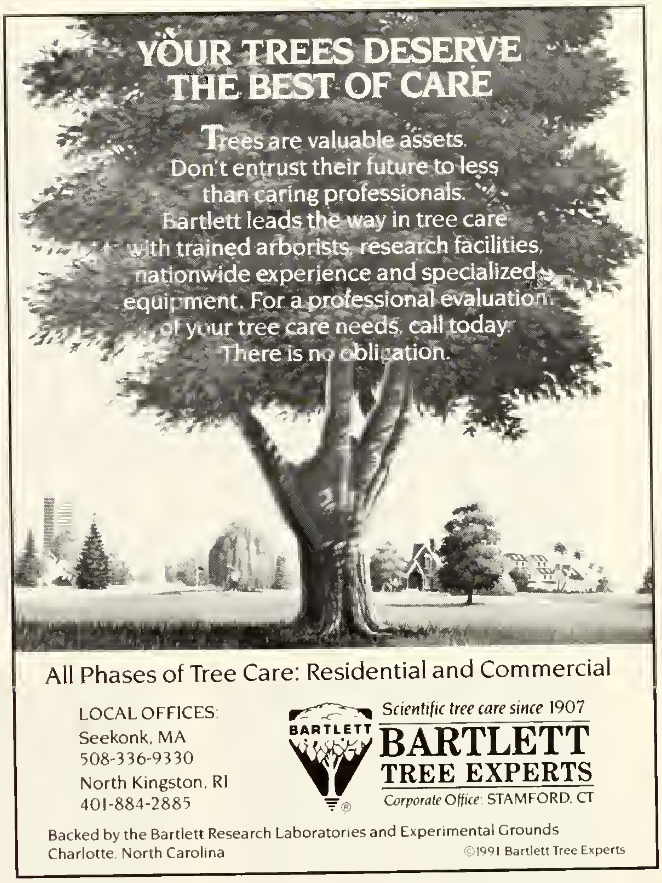
CFR=Case Fatality Rate = No. deaths/No. cases x 100

abundant fresh water resources in the world, large segments of those populations, especially the economically disadvantaged, remain without adequate drinking water or sanitation services.

Public health officers from the United States have declared, "... the principal route of transmission (ie, of cholera in this pandemic) was via municipal drinking water." Their studies also implicated contaminated food, locally raised vegetables and fruits and shellfish eaten raw.

Physicians who counsel overseas travelers are urged to consult with the physicians administering the state Travelers Clinics at Memorial Hospital (Dr S. Opal, 722-6000, Ext. 2545) or the Miriam Hospital (Dr GR Olds, 331-8500, Ext. 4075) for further information on cholera and related infections.

Stanley M. Aronson, MD



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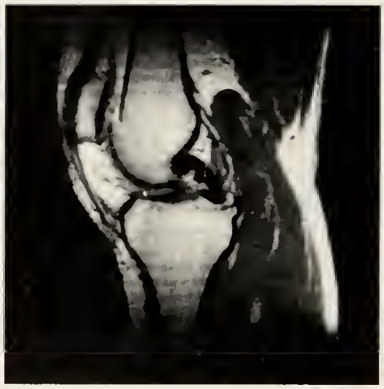

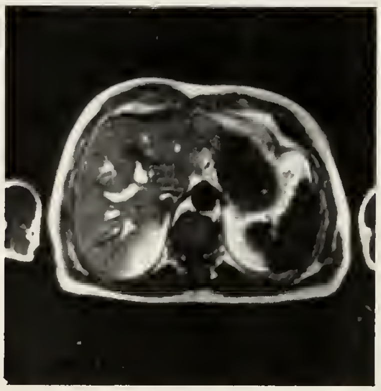

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Elimination of Preventable Blindness From Diabetes by the Year 2000

Elliot M. Perlman, MD
Ronald E. Smith, MD
Arnall Patz, MD

. . . diabetes is the leading cause of blindness among working-age Americans.

In no field of medicine is continuing medical education of physicians more critical than in the management of diabetes. Twelve million Americans have diabetes mellitus, and the disease knows no medical specialty boundaries. In addition to being a major cause of morbidity from multi-system complications, such as renal failure, neuropathy, and cardiovascular disease, diabetes is the leading cause of blindness among working-age Americans. It accounts for at least 12% of new cases of blindness every year in the United States. Diabetic retinopathy is often asymptomatic at its most treatable stage, emphasizing the importance of early diagnosis of this retinal complication. New information about diabetes emerges almost monthly as published in some specialty journals, making it mandatory for us to find better ways to keep up with advances in this field – the stakes are simply too high to do otherwise.

In response to the increasing importance of the overall problem of diabetes and diabetic retinopathy, and the availability of improved treatment regimens defined by published clinical trials results, the American Academy of Ophthalmology (AAO) has embarked on a long-term education project designed to more rapidly translate research findings to medical benefits for the American public. The new project – "Elimination of Preventable Blindness from Diabetes by the Year 2000" – or "Diabetes 2000" – was announced at the AAO's 1989 Annual Meeting.

Facts About Diabetic Retinopathy

The majority of diabetic patients have non-insulin dependent diabetes mellitus (NIDDM, Type II). Usually diagnosed after age 40, Type II diabetic patients may or may not be treated with insulin. Fewer patients have insulin-dependent diabetes mellitus (IDDM, Type I), which is usually diagnosed before age 30. Type I diabetics experience more frequent and severe ocular complications. After 5 years, 23% of Type I diabetic patients have retinopathy; after 10 years, almost 60% have retinopathy; and after 15 years, 80% have it. Proliferative diabetic retinopathy (PDR), the most threatening

ABBREVIATIONS USED:

AAO: American Academy of Ophthalmology
NEI: National Eye Institute
NIDDM: non-insulin dependent diabetes mellitus
PDR: proliferative diabetic retinopathy

Elliot M. Perlman, MD, is an ophthalmologist in private practice in Providence and president of the Rhode Island Society of Eye Physicians and Surgeons.

Ronald E. Smith, MD, is AAO Secretary for Continuing Education and National Project Director, Diabetes 2000.

Arnall Patz, MD, is past president of AAO and National Chairperson, Diabetes 2000.

form of retinopathy, is present in 25% of Type I patients after 15 years and often remains asymptomatic well beyond the optimal stage for treatment.

An estimated 700,000 Americans have proliferative diabetic retinopathy and 500,000 have macular edema.

An estimated 700,000 Americans have proliferative diabetic retinopathy and 500,000 have macular edema. The annual projected incidence of new cases of PDR and macular edema is 65,000 and 75,000 respectively. About 8,000 new cases of blindness a year in the United States are caused by complications from diabetes.

What Can Be Done

"Diabetes 2000" provides the means to close the gap between advances in research and changes in treatment patterns. While most physicians are aware of diabetic retinopathy, the AAO's goal now is to focus attention on the importance of early diagnosis and timely treatment of diabetic retinopathy based on the important advances of the last 5-10 years. For example, we now know that timely laser photocoagulation surgery can reduce the risk of visual loss from proliferative diabetic retinopathy by at least 50%. We know that timely laser photocoagulation surgery of diabetic macular edema can reduce the risk of moderate visual loss by 50%. We know that vitrectomy surgery can restore useful vision to some diabetic patients who have advanced diabetic retinopathy.

Effective Partnerships are Needed

As the working title implies, "Diabetes 2000" will be a long-term project aimed at a specific disease: diabetic retinopathy and its complications. Several phases are anticipated. Providing the latest research findings to ophthalmologists and other physicians who care for those patients is the first priority, followed by patient and public information. Initially, new advances and treatment guidelines for the medical and surgical treatment of diabetic eye disease will be emphasized through continuing education of ophthalmologists, other physicians, allied health professionals, residents, medical students, and specialists in diabetes-related education. In later phases, educational programs for diabetic patients and the public will be developed. Ultimately, improved eye care of diabetic patients is expected as a result of closer collaboration between the physician primarily responsible for the care of the patient's systemic illness, the patient, and the ophthalmologist. Since diabetic patients can be asymptomatic despite significant progression of diabetic retinopathy, the importance of a renewed and improved partnership between the ophthalmologist and the patient's primary physician is critical.

Because of the ambitious goal and long time-frame, many other medical organizations and public groups are involved in Diabetes 2000. Representatives from various medical specialties, government agencies, and other organizations devoted to problems of the diabetic patient have been invited to participate. Since diabetes is a complex, multi-system disease, whose overall management is the responsibility of physicians other than ophthalmologists, "Diabetes 2000" will stress involvement of other physicians and medical specialty organizations in the planning and implementation of the project. The importance of finding ways to develop effective partnerships between the patient's primary physician, the ophthalmologist, and the patient in the management of diabetic eye disease is a major goal. Another important aspect of the project is the identification and promotion of existing diabetes eye health programs around the country, such as the Center for Disease Control Diabetes Translation Project. The AAO will encourage ophthalmologists to participate in national, regional, and local programs that are already in operation. These programs are sponsored by such organizations as the American Diabetes Association, the Juvenile Diabetes Foundation, Lions Clubs, and others.

Rhode Island Ophthalmologists Are Participating

Educational materials are being developed and demonstration projects are underway in some states to encourage ophthalmologists and other physicians to participate in continuing education programs concerned with the overall management of diabetic retinopathy. A Preferred Practice Pattern on diabetic retinopathy is available through the offices of the American Academy of Ophthalmology (415-561-8500). This document provides the latest information concerning the management of diabetic retinopathy. The Rhode Island Society of Eye Physicians and Surgeons is actively involved in this national initiative. Ophthalmologists in Rhode Island are eager to help develop the necessary educational and service programs that will achieve this goal.

Diabetes 2000 will parallel a major diabetic retinopathy public information campaign recently announced by the National Eye Institute. The NEI's National Eye Health Education Program, which targets both diabetic retinopathy and glaucoma, is fashioned along the lines of earlier federal initiatives against smoking and high-blood pressure.

By continuously updating our medical knowledge and skills related to this multi-system disorder, and by forging partnerships between physicians in the effective and efficient management of diabetic patients, we have a unique and important opportunity. We can reduce preventable blindness from diabetes by the year 2000.

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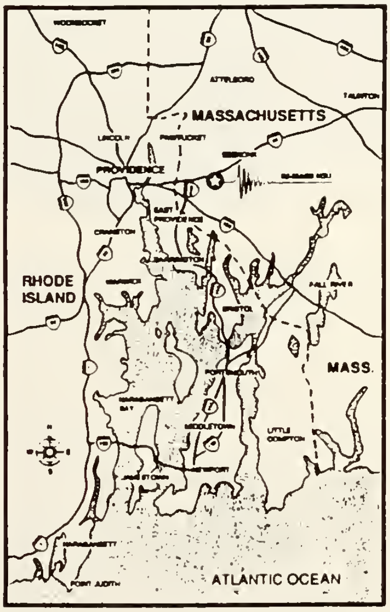

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What You Need to Know About Diabetic Retinopathy

Caldwell W. Smith, MD
Judith P. Feldman, MD, MPH

> ***. . . there is a tragic discrepancy between our abilities to preserve sight and the actuality of our doing so.***

Diabetic retinopathy is the leading cause of new blindness in America. Fortunately, significant advances have been made in our ability to successfully treat this condition. Unfortunately, many physicians outside the narrow specialty of ophthalmology are unaware of these advances, and therefore do not emphasize to their diabetic patients the importance of early and regular eye examinations. Because most diabetics see the physician who controls their diabetes on a regular basis, it is imperative that these doctors be informed of the tremendous advantages of early treatment in diabetic retinopathy.

Although laser therapy reduces the risk of visual loss from diabetic retinopathy by more than 50%, over 50% of diabetics with retinopathy severe enough to warrant treatment do not receive it.[1] Clearly, there is a tragic discrepancy between our abilities to preserve sight and the actuality of our doing so. The actual number of patients concerned is quite large. Since the prevalence of retinopathy is about 85 to 90% after 15 years duration of the disease, and since there are 35,000 known Rhode Islanders with diabetes and an estimated 26,000 with diabetes as yet undiagnosed, much of our population is at risk for visual loss.[2]

The purpose of this article is to bring the physicians in Rhode Island who are caring for diabetic patients up to date on what is known about diabetic retinopathy and our ability to treat it, in hopes they will become advocates for early and routine eye examinations.

The precise mechanisms by which diabetes leads to retinopathy are not completely elucidated. However, numerous humoral factors are abnormal in diabetes and along with thickening of the capillary basement membrane, lead to platelet and red blood cell aggregation with occlusion of small blood vessels. One of the earliest histologic changes in diabetic retinopathy is loss of the retinal capillary pericytes. Endothelial cell incompetence then leads to the formation of microaneurysms with leakage of serum and hemorrhaging in the retina. These changes of microaneurysm formation, retinal hemorrhages and retinal thickening from retinal vascular leakage constitute background or non-proliferative diabetic retinopathy. (Figure 1)

As the retinal vessels are further damaged they become occluded leading to retinal hypoxia. Cotton wool spots and venous beading are seen. Areas of retinal capillary nonperfusion may occur and look normal ophthalmoscopically. These areas are best identified with fluorescein angiography. (Figures 2 & 3) Tissue hypoxia leads to the growth of abnormal new vessels (neovascularization) on the retinal surface or into the vitre-

ABBREVIATIONS USED:

ADA: American Diabetes Association

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ous compartment (proliferative retinopathy). (Figure 4) These new vessels may bleed filling the eye with blood or contract and pull the retina away from the eye wall. Either condition may lead to profound visual loss.

Two sentinel papers guide our treatment of diabetic retinopathy. The first, published in 1976, reports the results of the Diabetic Retinopathy Study, a randomized, controlled clinical trial involving over 1,700 patients at 15 medical centers.[3] This National Eye Institute-sponsored study demonstrated the beneficial effect of laser photocoagulation treatment in proliferative retinopathy. Treated patients had a greater than 50% reduction in severe visual loss compared with untreated patients. Risk factors for severe visual loss based on the severity and location of neovascularization and the presence or absence of vitreous hemorrhage were established. Eyes at high risk for severe visual loss are those with neovascularization at the optic disc greater than one quarter to one third disc area in extent or eyes with any preretinal or vitreous hemorrhage associated with less extensive neovascularization at the disc or with neovascularization elsewhere greater than one half disc area in size. In these eyes the three year incidence of severe visual loss was reduced from 26.4% in untreated eyes to 10.5% in treated eyes. (Figure 5)

Eyes with less severe degrees of proliferative diabetic retinopathy have much less risk of severe visual loss. In these eyes the incidence of severe visual loss was reduced from 7% in untreated patients to 3% in treated patients.

Adverse effects of treatment include reduced night and peripheral vision, and in 10% of patients, a permanent decrease of one to two lines of visual acuity. These harmful effects assume greater importance when the risk of visual loss is low. Recent studies[4] have helped define at what level of severity treatment for proliferative retinopathy should be initiated. Eyes with mild to moderate, nonproliferative retinopathy are best followed up carefully without treatment. Eyes with high risk proliferative disease usually should not have treatment delayed. In eyes with severe nonproliferative or early proliferative retinopathy, scatter photocoagulation can be considered and the decision whether or not to treat tailored to the individual patient. Deferral of treatment carries little risk so long as treatment is applied as soon as high risk characteristics develop. Finally, in eyes with proliferative retinopathy and macular edema, initial focal photocoagulation (as described below) with delayed scatter photocoagulation reduces the incidence and severity of visual loss associated with the scatter photocoagulation.

The second landmark study, appearing in 1985, examined the treatment of diabetic macular edema.[5] This study, the Early Treatment Diabetic Retinopathy Study, was another National Eye Institute-sponsored, multi-centered, randomized, controlled clinical trial that compared no treatment to laser treatment for diabetic macular edema. In this study 1,490 eyes were followed without treatment and compared to 754 eyes treated with panretinal photocoagulation (the method for treating proliferative retinopathy) and 754 eyes treated with focal photocoagulation (small precise laser spots directed to the pathologic areas in the macula). In the untreated group, eyes with

Figure 1. Non-proliferative retinopathy demonstrating hemorrhages, microaneurysms, cotton wool spots and exudates.

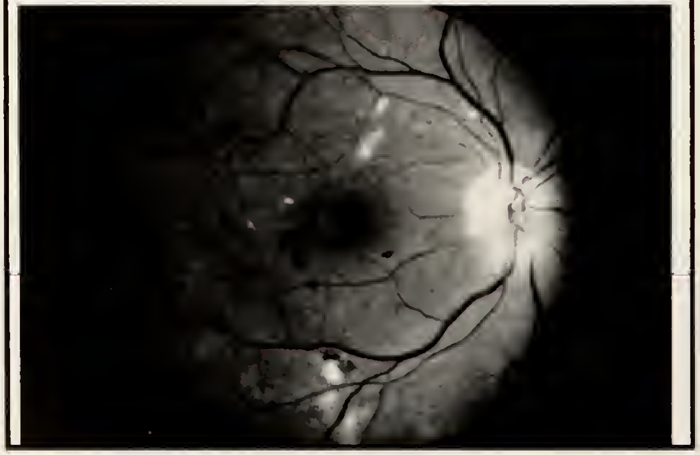
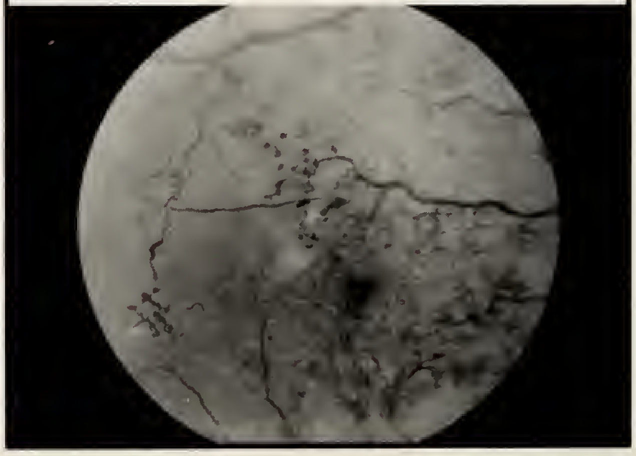


Figure 2. Severe retinopathy with normal appearing retina temporal to the macula.



"clinically significant macular edema" were most likely to go on to visual loss. Eyes with clinically significant macular edema have any of the following characteristics:

1. thickening of the retina at or within 500 microns of the center of the macula;
2. hard exudates at or within 500 microns of the center of the macula if associated with thickening of adjacent retina;
3. a zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula.

Focal laser treatment reduced visual loss from 24% in untreated eyes to 12% in the treated eyes at three years. (Figure 6) Few patients treated or untreated had *improvement* in visual acuity though improvement was more likely in treated patients. Side effects of treatment were minimal and no changes were seen in visual field or color vision.

With the efficacy of laser treatment proven, why aren't all diabetics for whom laser is indicated receiving it? It may be that physicians who give primary care to diabetics are unaware of these studies, and therefore do not emphasize the importance of eye care with their patients. For example, three years after publication of the Diabetic Retinopathy Study[6], a study showed that only 33% of primary care physicians would have recommended laser therapy for severe proliferative retinopathy and as late as 1987, many eligible patients who were seen by their primary care physicians were not receiving treatment.[7] In this study, 55% of eyes with proliferative retinopathy severe enough to warrant treatment never received it. Another reason involves the inherent shortcomings of direct ophthalmoscopy, especially through an undilated pupil. In proliferative retinopathy new vessels may be difficult to distinguish from normal retinal vessels and the area of retina scanned is quite small. Non-ophthalmologic physicians were found to have a greater than 50% error rate in diagnosing severe proliferative retinopathy, even through dilated pupils.[8] In macular edema, the transparent and microscopically thin retina is swollen. This thickening is usually impossible to see without stereoscopic viewing through a contact lens at the slit lamp biomicroscope. Direct ophthalmoscopy will often miss macular edema. For these reasons, even when the primary care physician examines the retina, she/he is likely to miss significant pathologic lesions.

These facts make it important that referral for eye care not be based upon the ophthalmoscopic appearance alone. Diabetics should receive regularly scheduled eye examinations regardless of their ophthalmoscopic appearance. The American Diabetes Association (ADA) guidelines for eye care in diabetics call for informing all patients that sight-threatening eye disease is a common complication of diabetes mellitus and is often present with good vision, and that early detection and appropriate treatment of diabetic eye disease greatly reduces the risk of visual loss. These guidelines call for routine eye evaluation in all Type I diabetics after five years duration of the disease and all Type II diabetics at the time of diagnosis. After the initial eye examination, ophthalmic exams should occur yearly unless more frequent exams are indicated by the presence of abnormalities. Controversy continues to exist as to which eye care doctors (optometrists vs ophthalmologists) are capable of detecting diabetic eye disease. Until this issue is settled, the primary care practitioner should be guided by the expertise and qualifications of

Figure 3. Fluorescein angiogram of patient in Fig. 2 demonstrating complete retinal capillary nonperfusion temporal to the macula in an area that looks normal ophthalmoscopically.

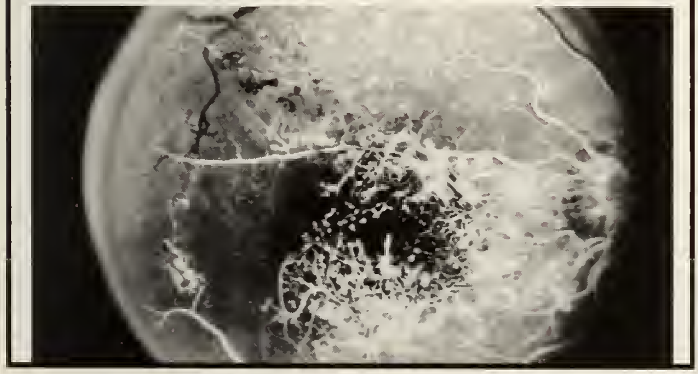
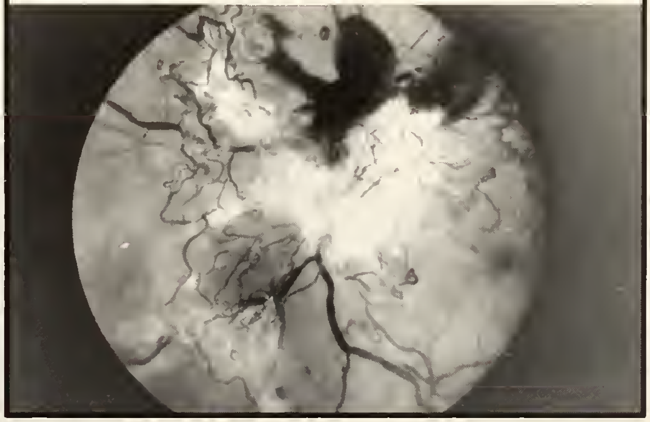


Figure 4. Proliferative diabetic retinopathy with vitreous hemorrhage.



the eye doctor to perform the examinations. When preproliferative changes, proliferative changes, or macular edema are present, the patient should be under the care of a retina specialist or other ophthalmologist experienced in the management of diabetic retinopathy. Diabetic women who are pregnant or are contemplating pregnancy should be seen by an ophthalmologist, since pregnancy may accelerate the progression of diabetic retinopathy. Table 1 summarizes these referral recommendations.

The effectiveness of treatment depends upon the accurate and timely detection of retinopathy. Physicians orchestrate their patients' care and thus are largely responsible for the accurate and timely detection of their patients' retinopathy. This is best accomplished when patients are examined for eye complications according to the ADA guidelines. Fundus examination through dilated pupils should be incorporated into all routine examinations and when significant findings are present, the patient should be referred for care promptly. Because of the likelihood that significant pathologic changes will be missed even when present, patients should be referred for routine eye examinations even when no retinal abnormality is found. The diabetic's personal physician must become convinced of the value of such examinations and insist that his patients receive them. Only timely ophthalmic examinations will enable us to apply the knowledge and techniques that we already possess to remove diabetic retinopathy from the top of the list of America's most frequent blinding conditions.

Table 1. Eye Examination Schedule

Age of Onset of Diabetes Mellitus	Recommended Time of First Exam	Routine Minimum Follow-up[a]
0-30	5 years after onset	Yearly
31 and older	At time of diagnosis	Yearly
During pregnancy	During first trimester	3 months

[a] Abnormal findings will dictate more frequent follow-up examinations.

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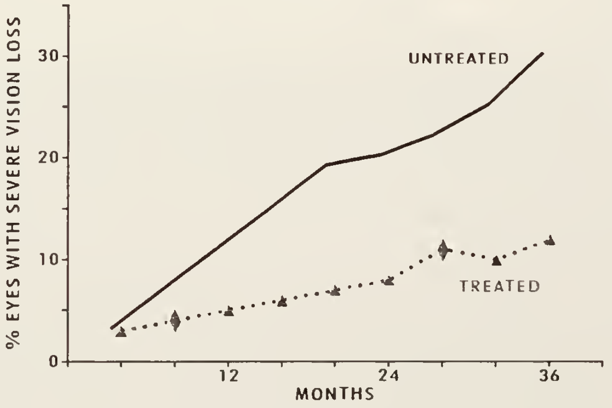
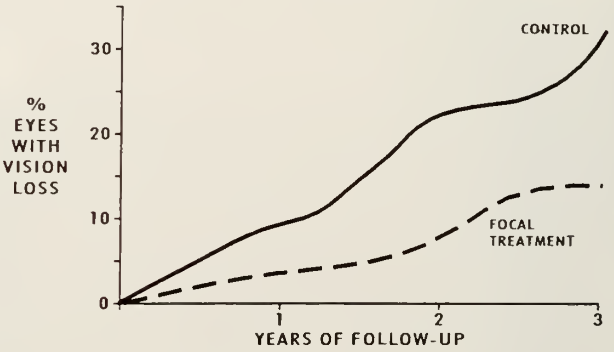
Figure 5. Cumulative rates of severe visual loss in eyes with severe proliferative retinopathy



: Cumulative rates of severe visual loss in eyes with severe proliferative retinopathy

Figure 6. Cumulative rates of visual loss in eyes with macular edema – treated and untreated



Cumulative rates of visual loss in eyes with macular edema - treated and untreated

Clinical Experience with Human Proinsulin in Eighteen Patients with Type I and Type II Diabetes Mellitus

Valerie A. Thomas, MD
R. Preston Lamberton, MD
Dennis S. Krauss, MD
Charles B. Kahn, MD

> ***Proinsulin appears to directly decrease hepatic glucose production . . . and, therefore, may be associated with a decreased incidence of hypoglycemia, potentially making it an ideal agent for the treatment of Type II diabetes mellitus.***

The pathogenesis of Type II or non-insulin dependent diabetes mellitus (NIDDM) represents a combination of three basic abnormalities: impairment of insulin secretion, insulin receptor or postreceptor site resistance, and increased hepatic glucose production.[1-4] Increased hepatic glucose production has been found to correlate with the level of fasting hyperglycemia[5,6] and likewise, a decrease in fasting hyperglycemia after therapy correlates with a decrease in hepatic glucose production.[7,8] One factor that potentially regulates hepatic glucose production is proinsulin, a single chain precursor of insulin, synthesized in the pancreatic beta cells. Endogenous proinsulin release generates plasma concentrations of 5-40% of the total levels of measurable serum insulin.[9-13] Since the technology has been developed to synthesize proinsulin from recombinant DNA, research has recently been undertaken with the hope of achieving better glycemic control for Type II diabetes mellitus, and possibly Type I as well, utilizing proinsulin therapy.[14,15] Proinsulin appears to directly decrease hepatic glucose production with a modest effect on glucose disposal, and therefore, may be associated with a decreased incidence of hypoglycemia, potentially making it an ideal agent for the treatment of Type II diabetes mellitus.

To ascertain whether diabetic patients (Type I and Type II) would respond to proinsulin with improved glycemic control and less symptomatic hypoglycemia, nine Type I and nine Type II diabetic patients, not previously treated with insulin, were randomized to treatment with either mixed beef-pork insulin or recombinant human proinsulin. This trial represents a portion of the national Lilly

ABBREVIATIONS USED:

DNA: deoxyribose nucleic acid
IRB: institutional review board
MBP: mixed beefpork insulin
NIDDM: non insulin dependent diabetes mellitus
PRO: proinsulin
SEM: standard error of the mean

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study ICBU involving 137 patients.

Methods

Nine Type I diabetic patients, three female and six male subjects with a mean age of 31.1 + 1.60 years, who had diabetes for a mean duration of 1.44 ± 0.29 years, and nine Type II diabetic patients with a mean age of 59.9 ±1.91 years who had diabetes for a mean duration of 9.67 ± 1.57 years (previously treated with insulin, oral agents, or diet alone), were enrolled in this study as part of the cooperative patient study sponsored by Eli Lilly and Company. Criteria for inclusion of Type II diabetic patients were fasting plasma glucose levels greater than 200 mg/dl and/or two hour postprandial plasma glucose levels greater than 300 mg/dl regardless of the presence of signs and symptoms. Patients had to have a fasting plasma glucose less than or equal to 140 mg/dl or a hemoglobin Alc level of 5.5% or less to demonstrate adequate control prior to enrollment for inclusion. Informed consent was obtained prior to enrollment in the study with standard IRB forms.

Patients were excluded if they received long term insulin therapy, received greater than seven doses of human insulin within seven days prior to enrollment, received past nonhuman insulin, were pregnant or planning pregnancy within the study time, had a life expectancy less than three years, received oncolytic therapy within one year, or had serum creatinine greater than 2.0 mg/dl acute or subacute cardiovascular diseases (including cerebrovascular insufficiency, myocardial insufficiency, peripheral vascular insufficiency, or congestive heart failure), detection of antibody titers to insulin or proinsulin, liver disease, alcohol and/or drug abuse.

Treatment group assignment was established through a randomization table. Patients received in double blind fashion, either human proinsulin for recombinant DNA origin (40 units, 10 mg/ml or 100 units 25 mg/ml of Iletin I N (NPH mixed beef pork insulin, 100 U/ml)). Supplemental regular insulin used were Humulin R (regular human insulin, 40 U/ml with m-cresol 2.5 mg/ml with no buffer) and Iletin I R (regular mixed beef pork insulin, 100 U/ml). Four Type I and four Type II patients were randomized to the proinsulin group.

Patients were given instruction and equipment required for home glucose monitoring and were requested to monitor plasma glucose levels twice weekly, (fasting and one hour postprandial), as well as whenever symptoms of hypoglycemia were present. Patients monitored urine ketones at home as well.

The goal of the study was to achieve a fasting plasma glucose level of 120 mg/dl without symptomatic hypoglycemia. This was to be accomplished with subcutaneous injections of either human proinsulin or mixed beef pork insulin (study insulins) prior to bedtime. If adequate glycemic control could not be achieved, additional injections of the same study material would be added to a maximum of four injections per day.

Patients underwent a "mixed meal challenge" whereby a fasting blood sample was obtained for glucose determination as well as a urine sample for assay of glucose and ketone via Ketodiastix determination. The subjects then drank 240 cc of Sustacal, which contains 34 grams of carbohydrate, and had a one hour postprandial blood sample collected for assay of glucose (at the time of each of nine office visits over a twelve month period) and C-peptide (on three visits only).

The patients were also required, during the 24 hours prior to the office visit, to collect in microcapillary tubes blood samples for glucose determination at eight predetermined times (fasting, one hour after the morning meal, prior to the noon meal, one hour after the noon meal, before the evening meal, one hour after the evening meal, prior to bedtime, and fasting the following morning). The assays were performed by Smith-Kline Laboratories using a Technicon Multichannel Analyzer.

Other testing included a blood lipid screen, prestudy antibody titers to insulin and proinsulin,[16] baseline hemoglobin A1c levels, complete blood count, antibody titers to E. coli polypeptide and complete urinalysis with microalbuminuria measurements. These assays were done at the Smith-Kline Laboratories using a Technicon Multichannel Analyzer for all chemistry panels, a Technicon Counter for all complete blood counts with a microscopic examination to determine differentials, and Ames urinalysis test strips with microscopic examination for all urine sediments.

Termination of the study occurred if the patient no longer required insulin therapy (in which case the patient continued to be followed), development of those conditions previously listed under exclusion criteria, a request of discontinuation by the patient, nonstudy insulin administered to the patient, lack of efficacy (failure to control signs and symptoms of diabetes mellitus), development of viral hepatitis, or two consecutive missed visits.

Early termination of the entire cooperative project was dictated by a statistically higher number of myocardial infarctions in the study group nationwide. Due to the limitation of the data available secondary to early termination, only a limited number of statistical analyses could be accomplished. All summed data are presented as means ± standard error of the mean. A chi square was applied to initial multiple sets, to determine if any statistical significance was present, followed by a paired t-test where applicable.

Results

In Table 1, weight, blood pressure, heart rate, and C-peptide levels are given for each of the patients on admission to the study. These data are presented in terms of Type I versus Type II and proinsulin (PRO) versus mixed beef pork insulin (MBP) patient groups.

In Tables 2 and 3 the plasma glucose values of each group, fasting and one hour postprandial, are presented. These data are given both at the beginning and end of the trial. All plasma glucose values decreased within study time with a greater decrease for the proinsulin groups. The fasting and one hour postprandial glucose values were similar for both Type I and Type II patients on proinsulin and mixed beef pork insulin. The overall chi square value was not significant, indicating that the randomization process via these parameters held true. The chi square after treatment was significant. When internally analyzing these data, statistical significance of improved plasma glucose values was reached for both groups on mixed beef pork regimen and Type I diabetic patients on proinsulin regimens. Statistical significance was not reached for Type II diabetic patients on proinsulin levels.

Table 1. **Admission Profiles of Patients**

	Weight ± SD (lbs)	**BP ± SD (mean)**	**HR ± SD (beats/min)**	**C-peptide ± SD (uU/ml)**
Type I				
PRO	163 ± 11.4	86 ± 9.2	85 ± 13	0.29 ± 0.27
MBP	160 ± 83.7	88 ± 25	82 ± 17	0.18 ± 0.15
Type II				
PRO	162 ± 35.7	97 ± 16	85 ± 6.6	0.45 ± 0.63
MBP	171 ± 39.5	99 ± 21	86 ± 24	0.55 ± 1.11
t-test p-values:				
Type I	0.939	0.871	0.762	0.449
Type II	0.715	0.870	0.926	0.865

Table 4 contains the means of antibody levels, for each enrolled subject, to human, beef, and pork insulin and to human, beef, and pork proinsulin at the onset and the conclusion of the study. There was no statistical significance either before and after the treatment period for the same study group, or before and after between study groups.

Discussion

The purpose of this study was to evaluate proinsulin as an alternative treatment for Type I and Type II diabetes mellitus. In Type II diabetes mellitus pathophysiologic defects lead to decreased peripheral insulin action which results in increased free fatty acid generation, gluconeogenesis, increased hepatic glucose output and increased plasma glucose levels.[6] The major abnormality of nonfasting hyperglycemia has been shown to be secondary to decreased peripheral glucose utilization.[1] Therefore, Type II diabetes mellitus can be seen as a combination of two distinct pathophysiologic mechanisms leading to both types of hyperglycemia, fasting and postprandial.

With hyperglycemia, impairment of insulin secretion results in further hyperglycemia leading to impaired endogenous insulin stimulation, termed glucose toxicity. Therefore, maintaining near eugylcemia (especially fasting) should lead to a better endogenous response and hence better glycemic control. The proposed benefit of proinsulin therapy was to obtain acceptable glycemic control (perhaps through its long half life) and also to lead to less hypoglycemia.

> ***The purpose of this study was to evaluate proinsulin as an alternative treatment for Type I and Type II diabetes mellitus.***

Proinsulin has been found to bind to insulin receptors with only approximately 10% binding potency of insulin and has a slower plasma clearance rate by approximately 30%.[19-21] Although proinsulin does possess some intrinsic bioactivity similar to insulin, most of these bioactivities are relatively weak (approximately 5-10% of insulin).[21-28] When proinsulin is administered subcutaneously, however, more than 90% is unchanged until it reaches the kidney where it is subsequently metabolized.[29,30] In vivo cleavage gives rise to several intermediate forms found to have glucose lowering properties between that of proinsulin and insulin.[29,30] Using a modification of the euglycemic glucose clamp technique, the clearance kinetics of the proinsulin molecule as well as its biologic effects were studied and compared with insulin. While a number of studies in animals and man have confirmed that the biological potency of human proinsulin is 4 U/mg after single doses, in all studies in which multiple doses of human proinsulin have been used the potency was found to be 5.6-5.7 U/mg. This pharmacological difference remains unexplained. For insulin the peak steady state concentration occurs in two hours with a half-life of five minutes, for proinsulin the peak steady state concentration occurs in greater than four hours with a two-component half life of 25 and 146 minutes.[13]

Proinsulin has been studied in nondiabetic subjects as well as in limited trials with Type II diabetics to ascertain its effects on peripheral glucose disposal and hepatic glucose production. Proinsulin was found to lead to decreased hepatic glucose production with slower onset of action than insulin, but with longer lasting effects varying inversely with the hormone concentration.[13,21] In comparison with insulin for a given level of suppression of hepatic glucose output, the human proinsulin has a smaller effect on peripheral glucose disposal.[13,21] The combination of these effects leads to a decreased fasting plasma glucose with a decreased incidence of hypoglycemia.[7] After study of ten nondiabetic subjects, proinsulin-mediated glucose disposal was found to be approximately 8% that of insulin, while proinsulin-mediated hepatic glucose production was found to be approximately 12% that of insulin.[21] Thus, in these ten nondiabetic subjects proinsulin was found to have a lesser hypoglycemic effect while also not generating hepatic glucose formation. Both of these properties are advantageous when treating diabetic patients.

Table 2. **Admission Plasma Glucose Levels (mg/dl)**

	Fasting + SEM	One Hour Postprandial + SEM
Type I		
PRO	306 ± 12.1	355 ± 31.3
MBP	266 ± 11.0	378 ± 18.2
Type II		
PRO	313 ± 9.12	366 ± 8.51
MBP	368 ± 13.4	396 ± 31.3

The study population presented here was well-matched within each Type I and Type II group with respect to age, blood pressure, weight, heart rate, and initial C-peptide measurement. Individual variability was to be eliminated through randomization. Variability between the response of Type I versus Type II was not an issue as these were examined independently. Both study insulins were shown to lower blood glucose in Type I and Type II diabetics. Proinsulin was not shown in this limited study to be advantageous.

The actual study format, giving one injection of study insulin at bedtime and then increasing as necessary from that starting point has been reviewed prior to this study in both animals and man. In these studies the effects were found to be additive and not synergistic in peripheral glucose disposal.[23,31-34] Some investigators found an advantage with proinsulin given one hour prior to insulin while others found no difference in the sequence of administration.[34] Of interest was the fact that hepatic glucose production was found to be completely suppressed with infusion of both insulin and proinsulin, and therefore additive versus synergistic effects could not well be documented.[34] However, better glycemic control was attained.

The reason for the discontinuation of the cooperative study involved the unexplained emergence of myocardial infarctions in the study (proinsulin) patients. During the ongoing reporting of complications, there were six myocardial infarctions, two fatal, in the proinsulin groups.[35] This number reached statistical significance

Table 3. **Plasma Glucose Levels After Treatment Period (mg/dl)**

	Fasting ± SEM	One Hour Postprandial ± SEM
Type I		
PRO	110 ± 6.13	195 ± 13.9
MBP	195 ± 19.8	243 ± 44.7
Type II		
PRO	175 ± 36.5	262 ± 44.7
MBP	183 ± 14.3	303 ± 23.4

Table 4. **Antibody levels to pork (PI), beef (BI), and human (HI) insulin and to pork (PPI), beef (BPI) and human (HPI) proinsulin at the study onset and conclusion**

	PI	**BI**	**HI**	**PPI**	**BPI**	**HPI**
Antibodies at onset of study						
Type I						
PRO	0.026	0.029	0.024	0.039	0.033	0.033
MBP	0.027	0.028	0.030	0.038	0.026	0.036
Type II						
PRO	0.023	0.030	0.028	0.033	00.029	0.043
MBP	0.028	0.030	0.029	0.035	0.030	0.041
Antibodies at conclusion of study						
Type I						
PRO	0.022	0.030	0.025	0.042	0.036	0;025
MBP	0.026	0.033	0.029	0.048	0.040	0.028
Type II						
PRO	0.028	0.031	0.031	0.039	0.033	0.032
MBP	0.029	0.034	0.029	0.040	0.034	0.032

*** Overall chi-square = 0.017 with p = 1.000 ***

and the central organizing committee discontinued the study pending further investigation. In a second trial with proinsulin there were three myocardial infarctions in the control (insulin) group, one fatal, versus none in the study group.[35] It is well known that the diabetic population is at higher risk for accelerated vascular disease including coronary artery disease and myocardial infarction. When this fact is coupled with the data of the second study revealing myocardial infarction only in the control (insulin) group, there remains much theoretical conflict as to whether all future trials with proinsulin should be banned.

Conclusion

The results as presented are noteworthy on several points. All patients appeared to improve and one must speculate whether this is a product of heightened awareness and education in the project population. Perhaps by requiring such close monitoring, patients became more conscious of their disease. The proinsulin groups for both Type I and Type II patients seemed to show greater improvement in diabetic control, although this was not statistically significant in this limited study.

Perhaps future investigation will prove proinsulin safe. It would be of great interest to determine if proinsulin therapy clearly improves glycemic control with a decreased likelihood of hypoglycemia. Another interesting application of proinsulin would be to use it as a single evening injection (aimed at reducing fasting hyperglycemia) coupled with a morning oral hypoglycemic agent (to treat postprandial hyperglycemia). In this way, Type II diabetes mellitus may be more easily controlled. The need for large doses of insulin, often seen in Type II diabetics, the possibility of antibody formation and the risks of hypoglycemia may be substantially reduced. Hopefully, continued research with this potentially efficacious treatment modality can soon progress and provide further options in the treatment of diabetes mellitus.

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The Mode of Presentation of Breast Cancer at Rhode Island Hospital: A Two-Year Retrospective Analysis

James Rost, BS
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Kay Wagner, MBA
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In our study we examined the initial presentation and method of diagnosis in women diagnosed with breast cancer in a geographic region where compliance with screening is 37%.

Breast cancer is the most common cancer occurring among women in the US afflicting one in every ten women.[1] In 1990 alone, it is estimated that 150,900 women will develop breast cancer with an estimated 44,000 female deaths in the same year. The incidence rate has increased 1% a year since the early 1970s and has increased from 85 per 100,000 in 1980 to 105 per 100,000 in 1986.[2]

Because of its insidious nature, breast cancer can develop and metastasize before it causes any signs or symptoms. Once abnormalities such as pain, nipple discharge or a palpable mass are discovered, the disease is often advanced and the prognosis has rapidly deteriorated. Because of mammography's ability to detect many breast cancers before even the early signs or symptoms are evident, it is recognized as an important screening procedure for women at risk for developing breast cancer. Several large-scale studies, including the HIP study[3] and the Breast Cancer Detection Demonstration Project (BCDDP)[4] have demonstrated a significant reduction in mortality in the screened populations. For example, when breast cancer is detected before the axillary lymph nodes are found to be involved, 74% of patients will survive ten years, whereas only 39% of women survive ten years if nodal metastases are found at the time of detection.[5]

As a result of these data, a major emphasis has been placed on the early detection of breast cancer in the symptomatic population. The American Cancer Society recommends monthly breast self-examination as a routine good health habit for women twenty years or older, a baseline mammogram for those between thirty-five and thirty-nine, a mammogram every one or two years for asymptomatic women aged forty to fifty, and yearly in women aged fifty-one and over. In addition, a physical examination of the breast performed by a physician is recommended every three years for women between the ages of twenty and forty and every year for those older than forty.[2]

Despite these recommendations from the American Cancer Society and other medical groups, screening for breast cancer is underutilized in Rhode Island[6] and the United States as

This paper by Rost and colleagues represents a Department of Community Medicine research project under the direction of Tom J. Wachtel, MD, who is Associate Professor of Community Medicine at Brown University.

ABBREVIATIONS USED:

BCDDP: Breast Cancer Detection Demonstration Project
NS: not significant

a whole.[7] In our study, we examined the initial presentation and method of diagnosis in women diagnosed with breast cancer in a geographic region where compliance with screening is 37%.[6]

Materials and Methods

We performed a retrospective study of women diagnosed with breast cancer at the Rhode Island Hospital during calendar years 1988 and 1989. A total of 296 subjects supplied by the Tumor Registry were available for review. We collected information pertaining to age, race, stage of disease[8] and family history of breast cancer directly from the RI Tumor Registry. The specific method of diagnosis was obtained by chart review and was divided into five categories: self discovery (complaint of a lump in a breast discovered during breast self-exam, or other breast-related complaints, such as pain or nipple discharge); mammography; physical exam performed by a physician; other symptoms; and unknown.

Results

The population studied included 296 women comprised of 282 whites (95.3%), 2 blacks (.7%) and 12 women whose race was not documented (4%) (Table 1). The ages ranged between 30 and 90 years with a mean of 64 ± 4 years. One hundred ten patients (37%) had no family history of cancer at any site while 52 patients (18%) had a positive family history of breast cancer. Thirty patients (10%) had a positive family history of cancer of another site and 104 patients (35%) had no documented family history.

Twenty-six patients (9%) were diagnosed with breast cancer in the in-situ stage. One hundred ninety-one patients (65%) were diagnosed with local spread smaller than 2.0 cm. Four patients (1%) were diagnosed with regional spread (2.0-4.9 cm). Sixty patients (20%) were diagnosed with breast cancer involving the regional lymph nodes. Twelve patients (4%) had evidence of distant metastases at the time of diagnosis and in 3 patients (1%) the stage of the disease was unknown.

Table 1. **Characteristics of 296 Incident Patients with Breast Cancer**

Race	**n**	**%**
White	282	95.5
Black	2	0.5
Other	12	4.0
Family History		
Breast Cancer	52	18
Other Cancer	30	10
No Cancer	110	37
Unknown	104	35
Stage		
In situ	26	9
Local (<2 cm)	191	65
Regional (2-4.9 cm)	4	1
Regional Nodes	60	20
Distant Metastases	12	4
Unknown	3	1
Method of Diagnosis		
Screening mamography	112	38
Self-discovered	98	32
Physical Exam	41	14
Symptom of Metastasis	5	2
Unknown	42	14

Patients who self-discovered their cancer were significantly more likely to have more advanced disease than patients whose breast cancer was detected by screening mammography. . . and tended to have more advanced disease than those whose cancer was detected by physical examination.

Mammography was the initial method of detection in 112 patients (38%). In 96 patients (32%) the initial signs or symptoms were discovered by the patient. Forty-one patients (14%) had their cancer detected during a physical exam by a physician. Five patients (2%) presented with systemic complaint secondary to distant metastases and 42 patients (14%) had no documentation of the initial method of diagnosis.

In order to assess the effect of age on disease stage at the time of detection, we grouped the first three stages into an early disease category and the last two stages into late disease category. The mean age of patients with early disease was 65 years whereas it was 61 years for women with late disease (p=0.04). Women who self-discovered their tumor were somewhat younger (mean age 62) than women whose tumor was detected by mammography (mean age 64) (p=0.29) and significantly younger than those whose tumor was detected by a physician's examination (mean age 69) (p=0.02).

There was no significant association between the presence of a family history of cancer and the initial method of diagnosis of the breast cancer.

The method of diagnoses was cross-tabulated with stage of disease dichotomized as above (Table 2). Patients who self-discovered their cancer were significantly more likely to have more advanced disease than patients whose breast cancer was detected by screening mammography (p=0.005) and tended to have more advanced disease than those whose cancer was detected by physical examination (NS).

Table 2. **Stage of Disease by Method of Diagnosis of Breast Cancer**

	Early Disease	**Late Disease**
Mammography	93 (83%)	19 (17%)
Physical Examination	32 (78%)	9 (22%)
Self-discovery	62 (66%)	32 (34%)
Disseminated	0 (0)	5 (100%)

$\chi 2=22.6$ p<.0001

Discussion

Our study included 296 women of which the vast majority (95%) were white and less than 1% were black. Given a 5% representation of black Americans in Rhode Island, one could infer that the preponderance of white women presenting with breast cancer in our study confirms the documented higher incidence of breast cancer in whites compared to blacks.[9] However, our sample may not be representative of the proportion of minorities in this community.

The mean age of women in our study is 64 years which is comparable to Brennan's reported median patient age of 60 years at time of diagnosis in the general population.[10] Seventeen percent of the subjects had a positive family history for breast cancer. These results are consistent with previous studies demonstrating that 18% of women with breast cancer have a positive family history of breast cancer.[11]

While stage of disease in our sample is comparable to other populations described in the literature when one considers early and late disease, some discrepancies should be noted within the two groups. Among patients with early disease, more patients had local spread in our group compared with Feldman[12] (65% vs 50%) and fewer had regional spread (1% vs 20%). Among patients with late disease, 19% of our patients had nodal involvement compared with 10% in Feldman's study, whereas only 4% had distant metastases in our study, compared with 10% in Feldman's study.

Our data imply that women with a positive family history of breast cancer are not seeking out methods of early detection (eg, mammography) any more frequently than their counterparts.

One decade ago, 80% of breast masses were found initially by the patient herself either accidentally or during purposeful breast self-examination.[13] Our data revealed that only 32% of breast cancers were currently detected in this manner, while 52% were detected by mammography or physical exam by a physician. This discrepancy could be due to the fact that Rhode Island women either are not performing breast self-examination, or that they are being screened more frequently by physical examination and mammography.

The group of women who self-discovered their breast cancer in our study is a heterogeneous one, comprising two subsets of women who either had performed regular breast self-examination or had accidentally detected a lump or other abnormality in their breast.

Women with early disease were older than women with late disease. This is consistent with the literature and may be explained by a more aggressive or more rapid disease progression in younger women. These younger women were also more likely to have self-discovered their breast cancer. Although younger women are more likely to perform breast self-examination and are less likely to delay contacting a physician when they discover a suspicious breast lump,[14] this advantage may be offset by the fact that older women have more frequent contacts with health care professionals and are more likely to undergo physical examination or be referred for screening mammography.

Social reasons may explain, in part, our finding that relatively older women have their breast cancer diagnosed by physical examination rather than by mammography. Older women are less likely to function independently, due to illness or limited financial resources which may result in fewer mammographies.

Our study reveals no significant relation between family history of cancer and the method of diagnosis of breast cancer. This finding confirms the observation that among women undergoing mammography, a positive family history of breast cancer was ranked as least important of eight factors that influenced the women to obtain the mammogram.[15] Our data imply that women with positive family history of breast cancer are not seeking out methods of early detection (eg, mammography) any more frequently than their counterparts. This is in spite of evidence that the presence of a family history of breast cancer increases one's risk of developing breast cancer.

Mammography and physical examination are associated with a significantly greater proportion of early disease than self-discovery ($p<.01$). Other studies have demonstrated that screening for breast cancer with mammography and physical examination is effective in detecting earlier stages of breast cancer.[16,17]

Screening by mammography and physical exam results in the detection of tumor with negative nodes in 90% of patients. The average tumor size is 1.1 cm when screened by mammography and physical examination compared to 3 cm when detected by the patient herself.[18] In addition, when self-discovered, tumors are associated with nodal extension in 55% of women.[18] Shapiro has shown that the combination of mammography and physical examination approach can reduce the death rate from breast cancer by 30%.[19]

Screening by mammography and physical exam results in the detection of tumors with negative nodes in 90% of patients.

Because all women are at high risk for developing breast cancer, and because screening procedures are available to detect the disease in its early stages, higher utilization of physical examination, mammography and breast self-examination could improve substantially the prognosis for women with breast cancer.

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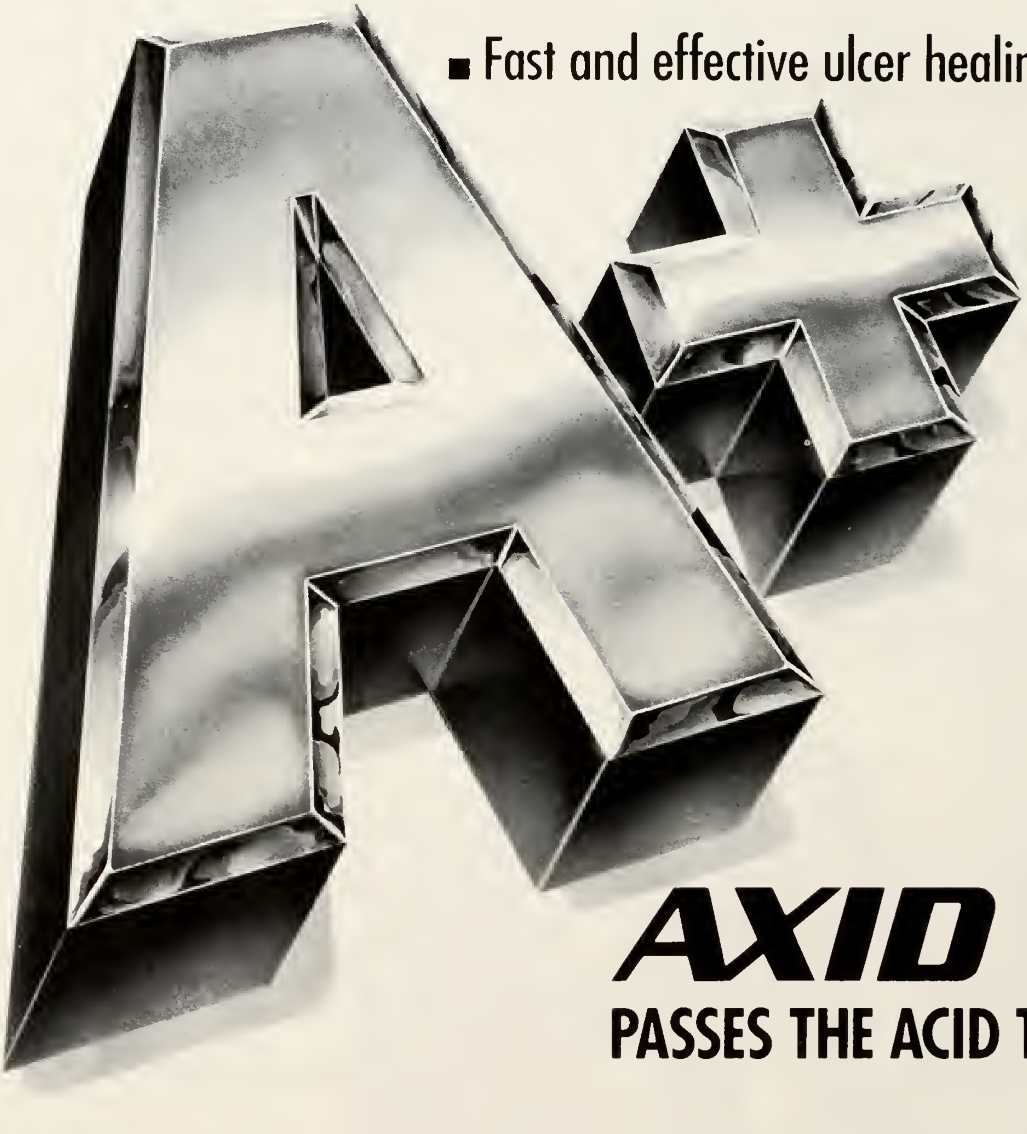

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3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests – False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions – No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility – A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects – Pregnancy Category C – Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use – Safety and effectiveness in children have not been established.

Use in Elderly Patients – Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions. Clinical trials of varying durations included almost 5,000 patients. Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine whether a variety of less common events were due to the drug.

Hepatic – Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular – In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS – Rare cases of reversible mental confusion have been reported.

Endocrine – Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic – Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental – Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity – As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other – Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage. Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

PV 2091 AMP
[091190]

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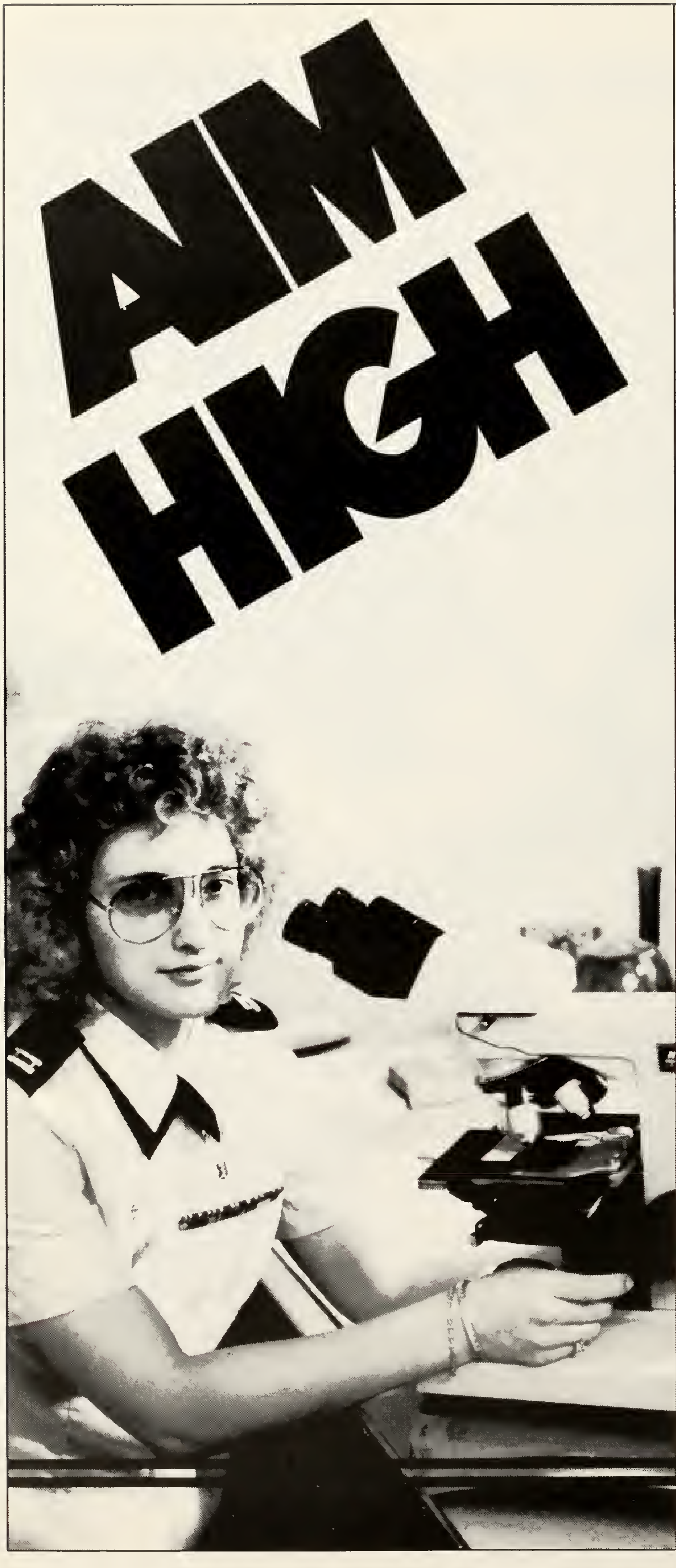

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AIR FORCE

Development of a Radioimmunoassay to Bradykinin Using Monoclonal Antibodies

Marc S. Weinberg, MD
Richard J. Solomon, MD
Marshall Posner, MD

> ***With the development of hybridoma technology, monoclonal antibodies can be produced which may distinguish between the kinin peptides.***

Kinins are vasoactive peptides implicated in the regulation of blood pressure, glucose uptake in muscle, and salt and water transport in the kidneys and intestines.[1,2] Polyclonal antisera to kinins have been developed and utilized in the radioimmunoassays (RIA) for measurement of kinins in various tissues and body fluids.[3-6] Bradykinin, lysyl-bradykinin and met-lysyl-bradykinin are major kinins found in urines. Kinin RIA employing polyclonal antibodies cannot distinguish between these kinin peptides and therefore the technique is very limiting in the interpretation of the data.

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With the development of hybridoma technology, monoclonal antibodies can be produced which may distinguish between the kinin peptides. Large quantities of monoclonal antibodies are easily and quickly obtainable. We report here preparations of monoclonal antibodies directed against bradykinin. This was the first effort at Brown University to successfully produce monoclonal antibody. Furthermore, to our knowledge this is a first attempt to aim for highly restricted specificity with the use of monoclonal antibodies to kinins. The utility of this monoclonal antibody in an RIA has also been investigated.

Materials and Methods

Purified ovalbumin was coupled to bradykinin using ECD-carbodiimide as previously described.[3] One hundred ug bradykinin in a bradykinin-ovalbumin complex (emulsified in Complete Freund's Adjuvant) was then injected intraperitoneally into BALB-C mice (Charles River Park, Kingston, RI). Six months later a booster injection in Complete Freund's Adjuvant (50 ug) was given. After four days, one mouse was sacrificed and the spleen removed. The spleen was sterilely teased apart and the resulting single-cell suspension fused with 40 x 10^6 cells for the HAT-sensitive murine myeloma cell line P3U1[7], using previously described methods.[8] Cells were immediately dispensed in 996-well microtiter plates at 0.2 x 10^6/well in 100 ul of medial containing HAT selection media. Supernatants were tested after 10 days of growth. Of 384 wells screened, 43, or 11.2% were positive for reactivity with bradykinin (total binding of 125-Iodine-bradykinin was 6.0% ± 0.3%). Selected positive wells were cloned twice by limiting dilution.

ABBREVIATIONS USED:

IgG: immune globulin G
PBS: phosphate buffered saline
RIA: radioimmunoassay

Total binding of the monoclonal antibodies with 125-Iodine-bradykinin was used to determine titers of antiserum. Displacement tracer by bradykinin, lysyl-bradykinin and met-lysyl-bradykinin was used to evaluate whether antibodies were capable of differentiating between the three peptides. Seven antibodies were cloned. Forty percent binding of the tracer was obtained from unconcentrated supernatant taken from several of the cell cultures. In order to completely characterize two antibodies, cloned hybridoma cell lines were injected into pristine primed BALB-C mice to produce ascites. Ascitic fluid was partially purified by precipitation with 50% (v/v) saturated ammonium sulfate. The precipitate was then redissolved in PBS and dialyzed against PBS 0.015% sodium azide. An immunoperoxidase assay was performed to identify the antibody isotype using cloned cell supernatants (Hyclone, Logan, Utah). Both antibodies were found to be of IgG-1 isotype.

The kinin RIA with polyclonal antiserum was identical to methods described previously.[3] Two antibodies, C5 and D9, were characterized after ammonium sulfate precipitation. Total binding was determined between monoclonal antiserum and 125-Iodine-bradykinin. Nonspecific binding obtained by substituting normal mice ascites for the antibradykinin serum ranged from 1-4% and was subtracted from all experimental data. The standard curve ranged from 25-750 pg of bradykinin. Total binding and B/Bo values produced by addition of various concentrations of unlabeled bradykinin, lysyl-bradykinin and met-lysyl-bradykinin were determined for each of the monoclonal antibodies. A normal human urine pool with 5 ug bradykinin/ml in HCl peptstatin, was used in each assay as an internal standard.

The inter-assay and intra-assay coefficients of variation of the human urine kinin pool were determined. The recovery of synthetic bradykinin added to the human urine pool was analyzed for C5 and D9. Increasing aliquots of the human urine pool were analyzed to demonstrate a linearity and lack of interfering substances in the urine. In order to evaluate the affinity of C5 and D9, scatchard analysis was performed for both antibodies using bradykinin and met-lysyl-bradykinin. The cross-reactivity between C5 and D9 and purified human low molecular weight kininogen and partially purified bovine kininogen was determined to evaluate the potential utility of this method for analysis of human or bovine kinin levels.

Results and Discussion

Seven hybridomas were cloned. Two antibodies, C5 and D9, were characterized after ammonium sulfate precipitation. Total binding was evaluated for all cloned monoclonal antibodies. None were capable of differentiating between bradykinin, lysyl-bradykinin and met-lysyl-bradykinin which displaced tracer equally.

We report here our success in the preparation of monoclonal antibody directed against bradykinin.

Total binding in the RIA was 24.9±1.5% (n=10) and 26.8±1.7% (n=11) for C5 (1:500 final dilution) and D9 (1:1000 final dilution), respectively. The standard curve was 25 to 50 pg for bradykinin, lysyl-bradykinin or met-lysyl-bradykinin. The Kd by scatchard analysis for C5 and D9 were 3.33 x 10^{-9}M (n=9) and 2.86 x 10^{-9}M (n=10), respectively for bradykinin. Similar KD values were also obtained for lysyl- and met-lysyl-bradykinin.

The inter-assay and intra-assay coefficients of variation of the human urine kinin pool (5 ug/ml) were 8.8% (n=12) and 7.4 (n=5) for C5 and 7.2 (n=6) and 7.2% (n=5) for D9, respectively. The recovery of bradykinin added to the human urine pool was 94.8±7.5% (n=3) and 113.2±15.6% (n=3) for C5 and D9. Increasing aliquots of the human urine pool were linear and parallel to the standard curve for C5 and D9.

Summary

We report here our success in the preparation of monoclonal antibody directed against bradykinin. We further demonstrate that the preparation is easier and less time-consuming compared to the preparation of polyclonal antibodies. The polyclonal antibody provides a ready source of the reagent very much required in the performance of the kinin radioimmunoassay. Limitation of this reagent was in the fact that it did not attain the desired specificity to distinguish between the kinin peptides. Nevertheless, it is interesting to note that the domains of recognition sites can be very similar for monoclonal or polyclonal response, particularly when the antigen is smaller (molecular size of about 1 Kd) as is the case with bradykinin.

Our laboratory produced the first monoclonal antibodies at Brown University. These antibodies were directed to bradykinin in BALB-C mice and could recognize bradykinin, lysyl-bradykinin and met-lysyl-bradykinin. Using this reagent it is possible to develop and validate an RIA which can be utilized to measure total kinins in tissues and body fluids. Although this antibody shows similar specificity as found with the polyclonal antibody, the ease and shorter duration of this preparation may make it a reagent of choice.

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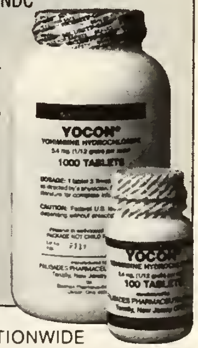

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1991 Annual Scientific Meeting of the Rhode Island Chapter of the American College of Physicians

The Fifth Annual Joint Meeting of the Rhode Island Chapter of the American College of Physicians and the Department of Internal Medicine of Brown University was held at the Omni Biltmore Hotel on Wednesday, March 27, 1991.

The agenda of the meeting included a presentation by Albert G. Mulley, Jr, MD, Associate Professor of Medicine, Associate Professor of Health Policy, Harvard Medical School; Chief General Internal Medicine Unit, Massachusetts General Hospital. Dr Mulley discussed "Practice Guidelines: Impact on Doctors and Patients." A panel discussion followed where the subject of "Who Sets Standards for Whom" was discussed. Panelists included Steven A. Wartman, MD, FACP, Professor of Medicine in Community Health, Department of Medicine, Brown University; Director, Division of General Internal Medicine, Rhode Island Hospital; Pamela A. Harrop, MD, ACP member, Clinical Instructor, Department of Medicine, Brown University; Jerome P. Kassirer, MD, FACP; Sara Murray Jordan, Professor, Associate Chairman, Department of Medicine, Tufts University School of Medicine, Editor Designee, *New England Journal of Medicine* and Albert Mulley, MD, the keynote speaker. The lecture and panel discussion addressed standards of care, use of protocol and outcome management.

The resident presentations were in both the oral and poster format. Clinical investigations and clinical vignettes were presented in each format. The abstracts of the orally presented material are included at the end of this article.

This year it was decided by the Brown University Residents Committee and the American College of Physicians Council that there would be no prizes for selected presentations, but that all presenters would be honored. This took the form of beautiful wooden plaques for those who presented orally and calligraphed certificates for poster presenters. All participants also received a full year's membership in the American College of Physicians, which includes a subscription to the *Annals of Internal Medicine.*

The program also included the awarding of the Irving Beck Award to Dr Janis Gailitis of Newport, Rhode Island. This award is presented to an outstanding internist and member of the American College of Physicians, Rhode Island Chapter for a long and sustained career of service to patients.

It was the impression of all participants that this was a particularly successful meeting with respect to the quality of data presented. Plans are currently being made for next year's event which will be held on Wednesday, April 8, 1992.

Fred J. Schiffman, MD

The Protective Effect of Warfarin on the Incidence of Myocardial Infarction

C. Alves, N. Freeman, J. Kirdar, A. Carvalho

Studies in the 1950s and 1960s designed to determine whether long term oral anticoagulation was effective in reducing the incidence of myocardial infarction (MI) or decreasing mortality from MI have not provided a consensus for treatment. The objective of this retrospective study was to assess the effect of warfarin therapy on the prevention of MI. We studied 231 patients, 113 receiving therapeutic doses of warfarin for at least two years, (mean=5.1 yrs), and 118 age and sex matched controls. Charts were randomly selected for review from the VAMC clinic population; all men over the age of thirty were eligible. Cardiac risk factors including hypertension, diabetes mellitus, smoking, hypercholesterolemia and obesity were recorded, as well as any documentation of known previous coronary artery disease. The diagnosis of MI during the study period was made by positive creatine kinase MMB fraction. The two groups were comparable in age and incidence of hypertension, diabetes, smoking, hypercholesterolemia, obesity and previous coronary artery disease. The number of patients in the warfarin group with MI was 6/113 (5.3%); the number of controls with MI during the five year review period was 17/118 controls (14.4%), $p < 0.05$. From this data, we conclude that warfarin therapy significantly decreases the incidence of MI (63% reduction) in men with high risk for coronary artery disease.

Inhibitory Effects of Suramin, Herbimycin A, and IFN-alpha on Human Melanoma In Vitro

C. Bowden, J. Clark, J. Marsella, P. Calabresi

The growth and metastasis of melanoma is controlled by various growth factors whose signal transduction is mediated, at least in part, by tyrosine kinases. In an attempt to assess the effect of inhibiting (either alone or in combination) growth factor-receptor interactions and internal signalling on the proliferation of melanoma cells, we used the XTT-PMS colorimetric assay to examine the effect of 72 hour treatment with Suramin (S) (0.2 & 0.4 mg/ml). Herbimycin A (H) (3.0 ug/ml), and IFN-alpha (I) (1.5 & 7.5 x 10 U/ml), on Mel-Tang, Mel-224, and Mel-5. (S), a polysulfonated naphtylurea, inhibits the binding of various growth factors to their receptors. (H) is a tyrosine kinase inhibitor. Interferons have been shown to interfere with proliferation of cells mediated by certain growth factors. (S), (0.2 & 0.4 mg/ml) inhibited Mel-Tang 9.4% and 23.1%, respectively. (S) at 0.2 mg/ml did not inhibit Mel-24 while 0.4 mg/ml inhibited Mel-24 7.9%. Mel-5 was not inhibited by (S). The combination of (S) and (I) increased inhibition of all three lines. (I) (1/5 x 10 & 7.5 x 10 U/ml) inhibited Mel-Tang 35.1% and 56.3% respectively. The addition of (S), (0.4 mg/ml), to the above concentrations of (I) increased inhibition to 46.8% and 69.0%. Mel-24 was inhibited 34.6% by (I) at 1.5 x 10 U/ml, and 51.3% by 7.5 x 10 U/ml. The addition of (S) (0.4 mg/ml) increased the amount of inhibition to 34.7% and 60.3% respectively. Mel-5 was inhibited 16.6% by (I) at 1.5 x 10 U/ml, and 55.9% by (I) at 7.5 x 10 U/ml. When (S), (0.4 mg/ml) was used in combination with (I) inhibition increased to 33.9% and 65.5% respectively. (H) (3.0 ug/ml) significantly inhibited all three lines. The respective inhibitions of Mel-Tang, Mel-24 and Mel-5 was 70.5%, 55.5%, and 60.6%. Combinations of (H) with the other inhibitors are being tested. Although the exact mechanisms for the growth inhibition mediated by these agents still needs to be determined, these studies suggest that inhibiting growth factor-receptor interactions and signal transduction may be a useful approach for the treatment of melanoma.

Catastrophic Sequelae of Pseudomembranous Colitis

Marc DeNuccio, Edward Feller

Life threatening complications of Clostridium difficile toxin-induced pseudomembranous colitis (PMC) are rare. We have recently seen four patients (Age range 58-78) in whom fulminant disease developed. Each patient had received prior antibiotic therapy.

Cases 1 and 2 developed mild crampy abdominal pain and watery diarrhea, and received Metronidazole for documented C. difficile toxin-induced disease. However, both patients subsequently deteriorated, developing increasing abdominal pain or tenderness, and received Metronidazole for culture proven PMC. Two weeks later, abdominal pain developed with leukocytosis and Vancomycin was added. Colonoscopy revealed severe, diffuse colitis with mucosal sloughing; total colectomy was required for refractory disease with concern for imminent perforation. Case 4 received 2 courses of Metronidazole after initial relapse of proven PMC. Oral Vancomycin was added when fever and diarrhea increased. After 3 days of therapy, diarrhea ceased and the colon became massively distended. Limited colonosocopy with decompressive suctioning and insertion of a rectal tube were performed, and Vancomycin was given via nasogastric tube. Distention diminished gradually, and symptoms resolved.

Delay in the diagnosis or institution of specific treatment may increase the risk of fulminant disease with perforation, toxic magacolon, or necrotizing colitis. Clinicians should be aware of the diverse spectrum and possible catastrophic complications of PMC.

Seroprevalence of Hepatitis C in China

AJ Luk, S Degli-Esposti, GL Wu, XH Guan, ZX Zhou, MA Zern, PM Wiest and GR Olds

The hepatitis C virus (HCV) is a major cause of non-A, non-B viral hepatitis in developed countries where the routes of transmission are similar to that of the hepatitis B virus (HBV). The main risk factors associated with parenteral transmission of HBV in developed countries are less important in some developing countries such as the People's Republic of China. We studied the seroprevalence of HCV in 1 urban and 1 rural area in China where we determined the prevalence of HBsAg in the random, unscreened population to be 13%. Using an ELISA (Abbott Laboratories) to detect anti-HCV, we tested 3 groups; blood donors, patients with chronic liver disease due to HBV, and patients with chronic non-B hepatitis. Patients with alcoholic, metabolic, drug-related or autoimmune liver disease were excluded on clinical grounds. In the city of Nanjing, 1 out of 57 random donors (1.7%), and none of 4 donors with elevated SCPT but negative for HBsAg, were positive for anti-HCV. 36 patients with chronic HBV-related liver disease (HBsAg positive) all tested negative for anti-HCV. Only 1 of 36 patients (6%) with evidence of chronic non-B hepatitis (HBsAg negative) were positive for anti-HCV. In rural Jishan Island, 1 of 92 random subjects was anti-HCV positive for (1%). Only the Jishan Island subject was positive for both HBsAg and anti-HCV. 1 of the 3 anti-HCV positive subjects had received blood transfusions. These preliminary results suggest that in China, (1) HBV is probably the major cause of chronic liver disease in endemic areas, and coinfection with HCV is rare, and (2) HCV does not appear to play an important role in non-B chronic liver disease; rather, another viral etiology for chronic liver disease (hepatitis F virus?) is possible.

Characterization of IgG Autoantibodies in Systemic Sclerosis

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Autoantibodies are present in several of the connective tissue diseases, including systemic sclerosis (SSc). Its pathogenesis remains obscure, but an autoimmune basis is suspected. It is characterized by abnormal fibrosis of the skin and internal organs. These patients also exhibit impaired cell mediated immunity: T lymphopenia, increased T4:T8 ratio, decreases suppressor-inducer and suppressor T Cell subsets, and depressed response to PHA. Autoantibodies to nuclear and nucleolar antigens are well characterized, but autoantibodies to cell membrane constituents are not.

We describe high titered IgG autoantibodies against T cell surface antigens in SSc. Sera from 29 patients were screened and revealed two patterns of reactivity: 1) 66% reacted (>1:50) with at least one of four malignant T cell lines; 2) 31% reacted (>1:50) to PHA blasts, but not ConA or PWM blasts (three of these reacted to PHA blasts but not the T cell lines). We have further characterized two prototypic sera, one with each pattern of reactivity. That each is an IgG has been confirmed by absorption of activity by Protein A. By Western blot analysis serum #1 recognizes proteins of approx. MW 35K, 60K, 85K on a malignant T cell line, and serum #2 recognizes 20K, 45K proteins on PHA blasts. Using immunoprecipitation techniques of TNP-surface labelled cells we will determine which of these proteins are surface components. These studies may help to establish the autoimmune mechanisms responsible for the T cell defects in SSc.

Carotid Sinus Massage by High Grade Lymphoma

Monique A. Anawis, Rochelle Strair

BF is a 75-year-old hypertensive woman who presented with a two week history of left frontal headache, nausea, dry heaves and near-syncope. In hospital, these episodes occurred on a daily basis with the above symptomatology associated with sinus bradycardia of 40 to 50 beats/min and severe hypotension with pulses usually nonpalpable on initial exam. Episodes varied in duration from 10 minutes to 1 hour, occasionally remitting after one mg of IV Atropine, and otherwise, resolved spontaneously. Symptoms were unassociated with chest pain, dyspnea, loss of consciousness, incontinence, or seizure activity. Despite sequential discontinuation of admission medications - Catopril, Metoprolol, and Furosemide - symptoms persisted. Physical exam was notable for a new I-II/VI faint, blowing systolic murmur at the left sternal border, and apex, and decreased S1. Neurological work-up included normal head MRI and normal EEG. Cardiac ECHO revealed a peak aortic gradient of 37 mm. Carotid noninvasives were essentially normal but were suggestive of a thyroid mass.

During evaluation, a left neck mass was detected. Ultrasound revealed a solid mass. Thyroid scan demonstrated a normal thyroid without uptake in the area of the mass. Thyroid function tests were within normal limits. Neck CT showed a noncalcified 5x5x13 cm mass wrapping around the left carotid artery. The patient refused MRI and surgical intervention, but consented to CT-guided needle aspiration of the mass. Final pathology revealed a high grade diffuse non-Hodgkin's lymphoma of the non-Burkitt's type. Tumor cells were positive for leukocyte common antigen and negative for vimentin, low molecular weight cytokeratin, and S100 protein, further supporting the diagnosis of lymphoma. Para-aortic adenopathy was detected on abdominal CT while bone marrow was free of tumor.

CHOP chemotherapy was instituted. Two days later, repeat neck CT clearly demonstrated reduction in tumor size, and, of greatest significance, the patient's symptoms of headache, nausea, bradycardia and hypotension completely resolved.

This is an extremely unusual case of a high grade lymphoma presenting with presumed episodic hemodynamic compromise secondary to tumor envelopment of the carotid artery.

Positive Mediastinal Gallium Scan in a Disease-Free Adult Post Chemotherapy for Hodgkins' Disease

Denise Burns, Fred J. Schiffman

Our patient is an 18-year-old woman who presented with nodular sclerosing Hodgkins' disease, stage IV, with involvement of right scalene and mediastinal lymph nodes and lung parenchyma. Pretreatment gallium-67 scan showed increased uptake in the mediastinum. The patient received six cycles of MOPP/ABVD chemotherapy. CXR and CT scans after cycle 1 of chemotherapy showed decreased mediastinal width and pulmonary masses. A gallium scan performed just prior to the last cycle of chemotherapy showed no abnormal uptake. In routine follow-up four months later, gallium scans showed increased activity in mediastinal and hilar regions and chest CT scans showed increased retrosternal mass. Since the radiological findings were initially accepted as reliable indications of residual active disease or relapse, aggressive therapy (including additional chemotherapy and/or autologous bone marrow transplant) was considered. However, prior to committing the patient to further treatment, a biopsy of the mediastinal mass was performed. Normal thymus tissue was found. She has continued to be in remission 18 months after treatment with subsequent negative imaging studies. The use of gallium scanning in the management of Hodgkin's and non-Hodgkin's lymphomas has been found to be useful both in diagnosis and in differentiating between residual active disease and benign mediastinal enlargement after chemotherapy. However, studies in children with lymphomas have shown increased gallium-67 uptake in the mediastinum several months after chemotherapy, due to benign thymic hyperplasia with no evidence of active disease. All of these patients were less than 15 years of age, and to date, there have been no other reported cases of this phenomenon occurring in adults. This case shows that while gallium scanning plays an important role in the follow-up of patients with lymphoma, the accepted practice of further treating adult patients who have residual masses and positive gallium scans after chemotherapy, may be premature. Such patients may benefit from biopsy of sites of suspected active disease prior to treatment.

Splenosis and Gastrointestinal Hemorrhage; Splenic Nodules Invade the Intestinal Wall

Ivan Coronado, Fred Schiffman

We present a patient who had profound GI blood loss of mysterious etiology until the time of surgery. A 48-year-old white man with history of type V hyperlipidemia and splenectomy at age 7 was admitted with melena. Physical exam was remarkable for orthostasis, benign abdomen and brown stool positive for occult blood. Hb was 5.5g/dl; MCV=89 and reticulocyte ct = 16.2%. An esophagogastroduodenoscopy, colonoscopy to cecum and tagged red cell study were normal. Abdominal angiography showed a hypervascular Rt renal mass and two colonic vascular lesions with active bleeding. Patient underwent laparotomy which revealed abdominal wall, mesenteric, small and large bowel splenuncules. Pathology showed multiple implants of splenic tissue on serosal aspect within the muscularis layer and also projecting intraluminally with ulceration of the mucosa. Other nodules did not penetrate the mucosa. Renal mass was found to be clear cell carcinoma. The patient's hemoglobin stabilized and he was discharged without further evidence of hemorrhage. This patient represents, to our knowledge, the first case of splenosis presenting as gastrointestinal hemorrhage involving the large bowel. Unanswered questions include: How such implants can grossly mimic native spleen? Does such a "mini spleen" begin from a single toti-potent cell liberated at time of trauma? What features of serosal surfaces lend themselves to nesting by splenic fragments? Is it possible for such tissue to reach areas in the body via lymphatic or vascular channels? What makes such tissue hypertrophy and ulcerate? Would such tissue be susceptible to embolization, sclerosis, radio-therapeutic or cytotoxic agents?

Dermatitis Herpetiformis: Vesicles, Villi and Vitamins

SL Denman, NJ Freeman

Dermatitis Herpetiformis (DH) is a pruritis vesicular skin condition associated with a gluten-sensitive enteropathy in 75% of cases. Proximal small bowel involvement may lead to iron and folate deficiencies without overt malabsorption. DH is felt to be autoimmune in nature and may be associated with other autoimmune diseases such as hypothyroidism and pernicious anemia. Therapy consists of Dapsone for the skin lesions. Dapsone denatures hemoglobin (Hgb) and causes a dose related hemolysis with anemia and increased folate requirements. A strict gluten free diet can improve the GI and skin manifestations and may decrease the requirement for Dapsone. Three patients with DH were referred to the Hematology clinic for anemia. Hemoglobins ranged from 9.5-13.5 g/dl. Compliance with diet and Dapsone dosages varied over time. Dapsone doses ranged from 100-400 mg/day. Two patients had a small bowel biopsy showing flattened villi. In review, 2 of the 3 patients exhibited significant hemolytic anemia with decreased haptoglobin 5-15 (NL 27-139 mg/dl), increased LDH 212-393 (NL<180 U/L), increased bilirubin 1.5-1.8 (NL<1.2 mg/dl), and increased MCV 94-123 (NL<80-94). These two patients were also found to be severely folate deficient 1.0-1.7 (NLS>2.5 mg/dl), iron deficient with a ferritin of 14-19.3 (NL>27 ng/dl), and B12 deficient 135-183 (NL>200 pg/ml). One patient was under treatment for clinically significant hypothyroidism. The third patient did not exhibit evidence of active hemolysis, folate, or B12 deficiency, on folate supplementation, but was markedly iron deficient with Hgb 9.5, MCV 78 and ferritin 11. B12, folate and iron levels corrected with supplementation in all patients. The Hgb stabilized at 12-13 g/dl perhaps suggesting an underlying anemia of chronic disease. Review of the literature and these three cases suggests that the clinical manifestations of DH is quite variable. All patients with DH treated with Dapsone should be on prophylactic folate therapy. Vitamin levels including folate, iron, and B12, and thyroid functions must be assessed on a regular basis to ensure adequate replacement. Dermatologists should be made aware of the diverse medical problems associated with DH.

Emphysematous Pyelonephritis

Hesham Hammouda, Bryson Ley, Steven Opal

Emphysematous Pyelonephritis (EP) is an uncommon disease but carries up to 90% mortality if not recognized and treated appropriately. Its presentation can be confusing.

This 68-year-old woman presented to our ER complaining of 72 hours of weakness, vomiting and maroon stools. Further complaints included urinary frequency and dysuria, but she denied abdominal or flank pain. She had no known previous medical problems, specifically no DM or GU problems. She was taking no medications. On exam BP=68/50, P=irreg, irreg @ 93-140, T-101.8. She had a non-specific abdominal exam, no CVAT and guiac positive stools. Lab evaluation revealed a HGB=15.9, WBC=3000, GLU=734, mixed metabolic acidosis, BUN/CR=67/2.0, LDH=3906, and U/A showing 4-6 WBCs and occasional bacteria. Abd flat plate showed stippled gas in the LUQ. A CAT scan confirmed gas in the parenchyma of the kidney and the perinephric area diagnostic of EP. She was initially treated with MEZLO/BENT/FLAGYL but switched to AMP when she underwent a Left Nephrectomy. The kidney was necrotic and culture positive for E. coli; there was no evidence of ureteral obstruction. On the 20th day she was discharged with her glucose controlled with glyburide.

Conclusions: 1. EP is a disorder seen most commonly in the elderly diabetic, especially in the presence of ureteral obstruction. 2. Sxs may overlap uncomplicated pyelonephritis or other acute intra-abdominal problems. 3. Enteric gram negative organisms usually E. coli are the most frequent causative organisms but Candidal and clostridial infections have also been reported. 4. Plain Abd films are often diagnostic but CAT scan is the definitive diagnostic procedure. 5. Combined Medical/ Surgical therapy is usually indicated.

A Case of Staphylococcus Aureus Bacteremia with a Cutaneous Primary Focus and Unusual Metastatic Complications

G Alan Kurose, Rodrigo Romulo

In the present antibiotic era, *S. Aureus* bacteremia (SAB) with an identifiable primary focus of infection is associated only infrequently with metastatic complications. We report a case of SAB with a cutaneous primary focus and multiple metastatic foci of infection in unusual locations with potentially severe morbidity.

A 61-year-old white male presented with neck stiffness, fever, and chills for two days. A month earlier he noted a subcutaneous nodule on his right shoulder which became inflamed, and four days prior to admission drained blood and pus. Past history included type II diabetes and anaphylaxis to penicillin. He denied alcohol use or HIV risk factors.

On physical exam the patient was mildly ill with a temperature of 103 degrees. Minimal cervical paraspinal tenderness was present. WBC was 12,800. Aspiration of the shoulder site was without yield. Cervical spine films showed mild degenerative changes. Serial lumbar punctures were negative.

In the hospital, fever and neck pain continued. Blood cultures were positive for S. Aureus sensitive to methicillin, and IV vancomycin was initiated. Cervical spine bone scan was compatible with degenerative disease. MRI with gadolinium, however, demonstrate dosteomyelitis and discitis at the C3/C4 level. Echocardiogram was negative. After four days of IV vancomycin, the patient developed panophthalmitis of the left eye which was treated with intravitreous amikacin, vancomycin, and dexamethasone. Blood cultures continued to be positive for *S. Aureus* and IV gentamycin was added. His right wrist became inflamed and an inflammatory nodule appeared over his right sternoclavicular joint with aspirates positive for *S. Aureus*. Operative drainage of the nodule revealed a soft tissue abscess without joint involvement. Sacral osteomyelitis was seen on gallium scan. Surveillance blood cultures became negative. Visual acuity was restored.

This patient demonstrated several unusual metastatic infections with the potential for severe morbidity. Vertebral osteomyelitis is a recognized complication of SAB but more commonly involves the lumbar or thoracic spine. The potential for progression to epidural abscess with cord compression mandates a high index of suspicion. Bacterial endophthalmitis is more commonly seen after trauma or surgery but can occur by hematogenous spread and cause blindness without prompt treatment. The patient's metastatic soft tissue abscess occurred in an unusual location, underscoring the fact that SAB can cause metastatic infection in any organ. This case demonstrates the potential of a localized staphylococcal infection with bacteremia to progress to multiple serous metastatic complications when antibiotic therapy is delayed.

Membranous Glomerulonephritis due to Thymic Carcinoma

James P. Osmanski II, Edward Wittels, Rogers Griffith, Rex Mahnensmith

A 43-year-old man developed bilateral pedal edema and 4+ proteinuria fifteen years after the diagnosis of squamoid carcinoma of thymic origin. The thymic carcinoma has been resistant to irradiation, and has spread to both lungs, pleura, pericardium, diaphragm, and liver despite a chemotherapeutic regimen which included cytoxan, prednisone, vincristine and procarbazine. At presentation, the blood pressure was 120/80 and pulse was 86. Rales were present in both lungs. The heart was normal. The liver was 17 cm by percussion. Pitting edema was found from ankle to groin. Serum albumin was 1.0 gm/dl. Twenty-four hour urine revealed 20 grams of protein and creatinine clearance of 112 cc/min. Inferior venacavogram and echocardiogram were normal. Renal biopsy showed large glomeruli with uniform, diffuse thickening of glomerular capillary walls with slight focal mesangial cell increase. The interstitium and vasculature were unremarkable. Immunofluorescence microscopy noted strong, fine granular staining for IgG and C3 along all glomerular capillary loops. Electron microscopy revealed small electron dense deposits along the epimembranous surface of the glomerular capillary basement membrane. These findings support the diagnosis of stage II membranous glomerulonephritis.

Thymoma is the most common thymic neoplasm, while thymic carcinomas account for less than 10% of all thymic neoplasms. Parathymic syndromes of the thymus occur in approximately 40% of patients with thymomas, myasthenia gravis, pure red cell aplasia, and hypogammaglobulinemia being the most among of these. However, paraneoplastic syndromes are rarely associated with thymic carcinoma.

Three cases of nephrotic syndrome have been reported in association with a thymoma, but biopsy tissue was reported in only one of these, and it showed minimal change disease. This is the fourth case of nephrotic syndrome reported in association with any thymic neoplasm, but is the first tissue diagnosed report of membranous glomerulonephritis in association with a thymic carcinoma.

Chronic GI Bleeding of Unknown Etiology in a Patient on Anticoagulation

LK Specthrie, N Freeman, S Uchman

A 60-year-old male presented for evaluation of chronic heme-positive stools while on Coumadin for neurologic indications. His history was remarkable for two bleeding gastric ulcers, one while on Coumadin, CAD, and an appendectomy at the age of 30. He complained of several months of abdominal cramps, watery diarrhea, and nausea. His abdominal exam was normal. Recent EGD, push enterosocopy of small bowel, and colonoscopy were unrevealing. Labs were remarkable for a Hgb of 12.7 mg/dl. His symptoms worsened, with an unchanged exam. Abdominal films were unremarkable. A bleeding scan revealed blood in the transverse colon after 20 hours. An UGI series with small-bowel follow-through was normal. Mesenteric arteriography showed several AVMs of the ileocolic artery. Repeat colonoscopy showed ileocecal AVMs, which were cauterized. His heme-positive stools continued, and he underwent an exploratory laparotomy. Multiple ileal masses were found, about 78 cm from the cecu, and resected. Pathology revealed carcinoid tumor with perineural and vascular invasion, and 3/3 nodes positive. Abdominal and chest CTs showed no metastases. The patient's symptoms worsened until he had 25-50 stools per day, with severe cramping. He also complained of hot flashes and light-headedness. He was started on somatostatin analogue, with relief of symptoms. 5-HIAA excretion was 4 mg/24h (nl 3-15 mg/24h).

Carcinoid tumor is a rare neuroendocrine malignancy usually presenting incidentally in the appendix. The second-most-common site is the ileum. Carcinoids elaborate mediators (5-HIAA, bradykinin, etc.) which cause the carcinoid syndrome (diarrhea, flushing, cramping) usually only after metastasis to the liver or lung. This case is unusual for its presentation, the multicentricity of the tumor, and the carcinoid syndrome without liver or lung metastases, or elevated 5-HIAA excretion (<5% of cases). It also demonstrates the need for aggressive evaluation of bleeding in a patient on anticoagulation.

Boerhaave Syndrome: The Hazards of Orange Juice

Lee Jayson Stone, Charles Sherman

An 80-year-old white male with a history of salt losing nephropathy and previous myocardial infarction, returned from his daily morning walk and drank a glass of orange juice. Immediately he became nauseous, retched several times without vomiting and acutely developed chest pain which radiated across the precordium. The patient also noted mild shortness of breath. On admission he was in mild respiratory distress with diaphoresis. Vital signs were: temperature 97.4, pulse 15, respiration 24 and BP=172/90. The rest of his physical exam was remarkable for: neck, mild venous distention and bilateral subcutaneous crepitus, and lungs: bilateral rales. Chest roentgenographs showed bilateral pleural effusions and pneumothoraces with mediastinal and subcutaneous air. Laboratories were significant for: CPK 687, LDH 317, and ABG on 2 liters; pH 7.23, pO_2=82 torr, pCO_2=27 torr, 94% saturation. An emergent gastrograffin video esophagram revealed extravasation of contrast material from the midesophagus into the left pleural space; the distal esophagus appeared normal. The patient underwent an emergency thoractomy where a 4 cm complete perforation of the mid-esophagus was found. No underlying esophageal pathology was noted. The tear was repaired and oversewed. The patient's course was remarkable for a pseudomonas aeriginosa pneumonia, but did not involve the development of abscess, or formation of empyema or esophagocutaneous fistulae. Boerhaave's Syndrome is often misdiagnosed and needs to be considered whenever a patient develops sudden chest pain following an episode of emesis, especially because of the increased mortality with delayed diagnosis. This patient represents a rare presentation of Boerhaave's Syndrome in that spontaneous esophageal rupture occurred in the mid- rather than the more common, distal, esophagus. The excellent clinical course was likely a result of the speed of diagnosis and treatment.

Fulminant Herpes Simplex Hepatitis in a Healthy 24-Year-Old Male

Alane Torf, Henry Bodenheimer

Herpes Simplex Virus (HSV) may cause fulminant hepatitis with a high mortality rate in pregnant and immunocompromised adults, but rarely in healthy adults. The following presentation describes a previously healthy male who developed fulminant, fatal HSV hepatitis after genital herpetic infection.

JM was a 24-year-old white male with no known medical history who presented to the emergency room with a five day history of fever, abdominal pain, nausea, vomiting, and diarrhea. He had a tattoo placed six weeks prior to admission and ate raw oysters ten days prior to admission. He denied intravenous drug use, toxin exposure, blood transfusions, and homosexuality. PE: Uncomfortable but healthy appearing male. VS: T 102.6, supine BP 110/60 with P92, upright BP 56/49 with P67, R 40. Skin showed erythema or spider angiomata. Abdomen was soft and flat with moderate RUQ tenderness, quiet bowel sounds, and a liver span of 14 cm without splenomegaly, fluid wave or shifting dullness. Genitalia were without lesion. Initial labs showed WBC=1,700 (nl diff), Hgb=18.2, Plt=23,000, PTA=30 sec, APTT=100 sec, Na=122, HCO33=18, BUN=32, Cr=1.5, AST greater than 10,000, ALT greater than 10,000, LDH greater than 10,000, and T bili = 2.5.

Course: Remarkable for rapid deterioration. six hours after admission, he became frankly encephalopathic and developed mucocutaneous petechiae and an upper GI bleed. Bleeding was refractory to transfusion therapy. He developed progressive respiratory failure and was intubated 18 hours after admission. He was flown to a liver transplant center for emergent transplant surgery. A donor liver (Hep C+) was available, but the patient died during the attempted transplant. Liver biopsy showed diffuse hepatic necrosis with viral inclusion bodies. Immunoperoxidase staining showed Herpes simplex virus infection. Subsequent history revealed that the patient had recently developed genital herpetic lesions.

Discussion: HSV in a healthy individual is a rare cause of fulminant hepatitis and is often not diagnosed until autopsy. Patients typically present with a 5-7 day history of a febrile illness with non-specific systemic complaints, leukopenia and minimal jaundice that progress to liver failure and death within days to weeks. No treatment protocols exist at this point. Early suspicion of Herpes simplex virus as an etiologic agent in fulminant hepatitis is thus critical to diagnosis and further study of this lethal complication of herpes infection.

MRI Manifestations of Cobalamin Deficiency

JP Tracey, Fred Schiffman

Neurologic abnormalities of cobalamin deficiency are well described. Symptoms, signs, and pathologic findings have been known for years. Spinal cord pathologic changes have only been described in specimens obtained from post-mortem examination. We discuss a patient whose pernicious anemia presented with neurologic manifestations and whose evaluation with MRI revealed a surprising finding which resolved with cobalamin treatment. A thirty-six-year-old woman was referred for evaluation of paresthesias. The patient had been well up to a year prior to admission when she developed Lhermitte's sign. Two months prior to admission, she developed numbness in fingertips which migrated to her arms then started in her feet. On admission to the hospital, the patient had a sensory level at C5 to vibratory and light touch. MRI of the cervical spine prior to admission showed a high intensity signal at C3-6. The patient was found to have a hemoglobin of 8.1 gm/dl with a mean corpuscular volume of 110 fl. B12 level was 9 pg/dl with a highly positive test for intrinsic factor antibody. The patient's symptoms and signs resolved with parenteral B12 replacement and follow-up MRI did not reveal a high intensity signal. The exact mechanism for the neurologic syndrome of cobalamin deficiency is unknown but the resulting pathology involves disruption of the myelination of the spinal cord and can be seen on post-mortem traverse section of the spinal cord. Changes usually begin in the cervicothoracic junction manifesting first by paresthesias then by further posterior column signs. Demyelination of the spinal cord (as in multiple sclerosis) can be seen as regions of high signal intensity on MRI examination. Our review of the literature suggests that this may be the first pre-autopsy correlation of neurologic symptoms and CNS pathology in cobalamin deficiency.

TB or Not TB–That is the Question

Ariane Urlich, E. Jane Carter

An 18-year-old college student born in Thailand, presented with a two-month history of nonproductive cough. He denied fever, chills, shortness of breath, and chest pain. He admitted to mild fatigue and a 10-pound weight loss without change in appetite. PPD performed at college matriculation (2 months prior to symptoms) was negative. He denied smoking, excessive ETOH intake, and HIV risk factors. There was no history of recent travel, pet contact or allergies. Neither a 10 day course of erythromycin nor bronchodilator therapy relieved his symptoms. Mild DOE and sputum production developed. Physical examination revealed a tall, thin male in no respiratory distress. He was afebrile. There was no adenopathy. Chest examination revealed equal excursions with crackles half way up the left. The right lung was clear. The remainder of the exam was normal. Laboratory revealed a normal CBC with 6% eosinophils. CXR revealed a diffuse reticulonodular pattern more prominent on the left. Cold agglutinins were positive at 1:16. Viral titers (Influenza A,B; Adenovirus; Mycoplasma) were negative. Sputum smear for AFB was negative. Repeat PPD and anergy panel were negative. HIV serology was negative. PFT revealed mild combined obstructive and restrictive disease. DLCO was 50% of predicted. Oximetry revealed desaturation at low level exercise. Bronchoscopy with bronchoalveolar lavage was performed. The mucosas of the entire tracheobronchial tree revealed a cobblestone appearance. Thin, nonpurulent secretions with airway erythema was noted throughout the left lung. Lavage analysis revealed a combined neutrophilic and eosinophilic alveolitis. Bronchial biopsy demonstrated non-caseating granulomas, AFB smear negative. Bronchial wash as well as post bronchoscopy sputa were positive for typical AFB. Institution of antituberculous therapy resulted in resolution of symptoms.

The incidence of tuberculosis is increasing, not only in RI but also throughout the US, due to a combination of factors: foreign immigration policy, ease of worldwide travel, the AIDS epidemic, and medical complacence. A high index of suspicion is required to guide the evaluation for this disease in the appropriate setting despite factors such as unusual clinical and roentgenographic presentations and negative skin testing.

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

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The Rhode Island Health Care System and Rhode Island's Elderly

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In 1990, the Rhode Island health care system cost a total of $2.5 billion, or about $2,500 per person.

Rhode Island's Health Care System

An elaborate and expensive health care system cares for nearly one million Rhode Island residents. Aging 2000's research study focused on the population over age 65. Yet, innovations that succeed in providing high-quality care for senior citizens can eventually point the way to improving the health care system for everyone.

In 1990, the Rhode Island health care system cost a total of $2.5 billion, or about $2,500 per person. Most of these funds are spent in hospitals, physician's offices and nursing homes. Together, they account for 75% of the money spent on health care annually in Rhode Island (Table 1).

Twelve acute-care hospitals, two private psychiatric hospitals, one public psychiatric hospital and two state-run chronic-care hospitals serve the state. The amount spent on hospital care in Rhode Island in 1990 totalled $999 million, or 39% of the total health-care bill.

The largest funder of hospital care is Medicare. Private health insurance covers hospital bills for most younger patients, and those with no coverage either pay out of pocket or the hospital provides the care without compensation.

Approximately 2,600 doctors practice medicine in Rhode Island. Physician services in 1990 cost a total of $654 million, 26% of the total cost of the health-care system.

The average Rhode Islander visits the doctor slightly more than three times a year. More than three-quarters of the population (76.1%) see a physician at least once a year.[1] According to a 1985 survey by the state Department of Health, Rhode Islanders report fewer visits to physicians than the national average. Men reported an average of 2.7 visits per year (national average, 3.9 visits). Women reported 3.6 visits (national average, 4.9).[2]

One hundred and five licensed nursing homes operate in Rhode Island providing 9,958 beds and account for $245 million in health care expenditures, 10% of the total. Nursing home patients represent an even larger portion of the cost, however, because of frequent hospitalizations, medications and other needs.

Nursing home care costs an average of about $28,000 per resident per year. Medicaid is the primary source of funding for nursing home care in Rhode Island. Some elderly people divest their assets in time to qualify for Medicaid, and others enter nursing homes paying privately, but "spend down" to Medicaid eligibility levels while living in the nursing home. In 1987, Medicaid paid for 71.3% of all nursing-home patient days. Resi

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Aging 2000 is sponsored by the Interfaith Health Care Ministries, and is dedicated to pursuing progressive care for Rhode Island's elderly. Aging 2000's detailed report on elderly care in Rhode Island is due to be published in early fall. For information, contact Aging 2000 at 56 Pine Street, Providence, RI 02903; or call (401) 421-5990.

dents or their families paid for 26.4% of the total days. Other insurance companies paid for the remaining 2.3%.

> ***Physician services in 1990 cost a total of 654 million dollars, 26% of the total cost of the health-care system.***

Rhode Island residents fill an estimated six million prescriptions for medication each year through two hundred retail pharmacies in the state. Retail prescription drugs in Rhode Island cost an estimated $108 million a year, about 5% of health-care costs. An estimated 50% of this cost is covered to some extent by insurance. Patients pay for the rest. A small percentage of Rhode Island residents who receive care through their health maintenance organizations or comprehensive health plans obtain medication there as well. Others have insurance that covers part of the cost of prescription drugs. Medicaid pays the cost of pharmaceuticals for its clients. The Rhode Island Pharmaceutical Assistance for the Elderly program pays for prescription drugs for elderly residents who meet income guidelines.

In 1991, just over 839,000 Rhode Island residents carried health insurance, not counting a small number who are covered by out-of-state companies.[3] The total cost of insurance and HMOs was over $99 million in 1990, about 4% of the total cost of the health care system.

Rhode Island's 15 Medicare-certified home health agencies provide skilled nursing care and professional assessments for patients, primarily those over age 65, in their homes. Five hospice programs also operate programs independently or through visiting nurse associations. Medicare covers skilled home care in most cases but for a limited number of visits and for a limited time. The average charge for nursing service ranges from about $65 to $75 a visit. An additional 53 home-care agencies provide homemaker and home-health aide services. Patients who require long-term or custodial care in their homes find few resources to help pay for it. For income-eligible clients who can be served through a state program, agencies such as the Department of Human Services or Department of Elderly Affairs refer clients to home-care agencies under contract with the state. The agency appoints a case manager to oversee services for those clients.

Table 1. **The Rhode Island Health Care System Costs**

	Costs ($MM)		**%**
Hospitals	999		39
Physicians	654		26
Nursing Homes	245		10
Dentists	145		6
Prescription Pharmaceuticals	108		4
Insurance Firms & HMOs	99+	(1)	4
Home Health Care & Homemaker Agencies	92		4
Non-Physician Practitioners	49		2
Laboratories	29		1
Public & Private Ambulance Companies	24		1
Departments of Health & Business Regulation	17		<1
Community Health Centers	13		<1
Department of Elderly Affairs	13		<1
Medicaid Administration	12		<1
Medicare Administration	10		<1
Self-insured Firms	7		<1
Renal Dialysis Centers	7		<1
Hospice Care	3		<1
Managed Care Reviewers	3		<1
TOTAL	$22,529	(2)	100

(1) Excludes out-of-state insurance firms

(2) Does not include approximately $97 million spent by the state/federal Medicaid program on group homes and other services for the mentally retarded/developmentally disabled population.

Hospices, ambulance companies, home-based infusion therapy providers, surgery centers, suppliers of durable medical equipment, rescue services, rehabilitation centers, walk-in emergency health centers, laboratories and a host of other providers, such as sheltered care homes, adult day care centers, and the state facilities, round out the Rhode Island health-care system. The state departments of Health, Elderly Affairs, Mental Health, Retardation and Hospitals, Human Services, and Children, Youth and Families all also provide health programs.

Despite efforts and massive expenditures to meet the health needs of most residents responsively and effectively, the Rhode Island health-care system has problems. Major lapses occur in both continuity and access to care. The system inefficiently duplicates some services and fails to coordinate others. In many cases, it fragments care so that no single provider is positioned to grasp the full condition and situation of the patient and act to alleviate problems. The elderly populations are unfortunately among the most vulnerable to these myriad, ongoing problems.

Rhode Island's Large and Growing Elderly Population

Rhode Island already ranks as one of the nation's "oldest" states, and its population is aging at a rapid pace. In the 1990 census, Rhode Island tied with West Virginia for the distinction of having the second highest proportion of residents over 65 years of age. Florida has the highest proportion of elderly residents, but Rhode Island has the highest proportion of people aged 85 or over.[4]

In 1990, over 150,000 Rhode Island residents were 65 or older, about 15 percent of the population.[5] By the year 2000, that number is expected to climb to more than 166,000. The most dramatic increase is expected among those age 75 and older, a group that will grow by 32%. In contrast, the state's young-adult population (ages 25 to 34) will decline from about 180,000 to 138,000 people, a 23% decrease.[6]

The Rhode Island population over age 75 includes 21,956 white males and 45,739 white females (United States Census Bureau) but only 688 males and 1,166 females who are members of racial minorities.

Part of the reason for the low numbers of minority elderly, both ethnic and racial, lies in the life circumstances of those groups. Minorities are more likely to have low socio-economic status in the United States, which poses added health risks and limits access to medical care. Blacks have a shorter life expectancy than whites, a fact that may be caused in part by inadequate access to health care among members of racial minorities. Blacks are also at greater risk for certain illnesses, such as hypertension.

Table 2. **Elderly Portion of Total Healthcare System[1] Costs in Rhode Island**

	Total Costs ($MM)	Elderly Costs ($MM)	Elderly Costs as % of Components
Hospitals	999	589	23
Physicians	654		
Home Health Care	20		
Non-Physician Practitioners	49		
Laboratories	29		
Public & Private Ambulance Companies	24		
Renal Dialysis Centers	7		
Hospice Care	3		
Nursing Homes	245	238	97
Dentists	145	1	1
Prescription Pharmaceuticals	108	41	38
Insurance Firms & HMOs	99	12	12
Homemaker Agencies	64	54	85
Departments of Health & Business Regulation	17	3	18
Community Health Centers	13	<1	0
Department of Elderly Affairs	13	13	100
Medicaid Administration	12	3	25
Medicare Administration	10	9	90
Self-insured Firms	7	<1	0
Managed Care Reviewers	3	<1	0
TOTAL	$2,529	$963	38

[1] Some Medicare dollars pay for the care of disabled, non-elderly people who are covered under Medicare.

Utilizing Rhode Island's Health Care Services

While some Rhode Island residents will spend their later years in comfort and good health, others will spend the last years of their lives in poverty or poor health with impaired functioning. Between 15,000 and 20,000 people over age 65 in Rhode Island have been diagnosed as having Alzheimer's disease or some related form of dementia.[7] An estimated 43% of Americans who turned 65 in 1990 will spend time in a nursing home at some point during their remaining years.[8]

Elderly patients account for over half the patient census in Rhode Island's acute-care hospitals. Medicare patients occupy 65% of all coronary-care beds, 61% of all intensive care beds and 45% of all routine-care beds.

> ***An estimated 43% of Americans who turned 65 in 1990 will spend time in a nursing home at some point during their remaining years.***

Physicians, therapists and visiting nurses spend an increasing proportion of their time caring for patients over age 65. Thirty percent of all prescriptions are written for people over age 65, and that proportion is expected to jump to 50% by the year 2000.[9]

Who Pays for Elderly Care?

There is no doubt that the system is extremely expensive. In 1990, an estimated $963 million was spent in Rhode Island on health services for the elderly, 38% of total costs and an average of $6,400 for each person over age 65 (Table 2). Public funds paid an estimated $565 million of that amount, approximately $3,767 for each elderly resident (Table 3).

Table 3. **The Publicly Financed Portion of Elderly Healthcare Costs in Rhode Island**

	Total Elderly Costs	Publicly Financed Elderly Costs	
		($MM)	%
Hospitals	589	404	69
Physicians			
Home Health Care			
Non-Physician Practitioners			
Laboratories			
Ambulance Companies			
Renal Dialysis Centers			
Hospice Care			
Nursing Homes	238	119	50
Dentists	1	0.1	10
Prescription Pharmaceuticals	41	11	27
Insurance Firms & HMOs	12	0	0
Homemaker Agencies	54	3	6
Depts. of Health & Business Regulation	3	3	100
Community Health Centers	<1	<1	<1
Department of Elderly Affairs	13	13	100
Medicaid Administration	3	3	100
Medicare Administration	9	9	100
TOTAL	963	565	59

Almost all federal Medicare expenditures and half of the budget for the state Medicaid program (known as "Medical Assistance") pay for the treatment of elderly people. Neither Medicare Part A nor Part B covers all health-care costs, however. Many Rhode Island residents purchase a "medi-gap" policy from a private insurance company to cover the co-payments and deductible costs. The cost of these policies has risen sharply over the last several years, however. "Blue Cross 65," for example, costs $390.72 per year for one person in 1984 and $655.80 in 1990.[10]

The state and the federal government each contribute roughly half of the Medicaid budget. In Rhode Island, Medicaid covers 30,000 elderly people with incomes up to $6,700, which is above the federal poverty level. In some ways, the State's Medicaid program represents a generous medi-gap policy for the elderly. It pays for services not typically covered by private medi-gap policies such as optometry, podiatry, durable medical equipment, home-health care, nursing-home care and prescription drugs. Yet the program is limited in other ways. Medicaid payment rates to doctors and institutions are substantially lower than Medicare rates, and many doctors choose not to provide service to Medicaid clients since the payments are so low.

Where Do Rhode Island's Elderly Live?

As care needs grow more burdensome, the elderly and their families come to crossroads. The lack of affordable programs to help people continue living in their homes forces a choice: They must trade in the amenities of home for the services of a more structured environment, or stay where they feel most comfortable and forego the care and safety they need.

Most elderly live in single-family houses, multi-family houses and apartments – the same places most non-elderly people live. In addition to those living in the community, elderly Rhode Islanders live in a range of structured settings including sheltered care, nursing homes, long-term care hospitals and life care communities.

Most elderly people prefer to remain in their homes. A 1989 American Association of Retired Persons survey confirmed this fact. Eighty-six percent of respondents over the age of 55 expressed the desire to stay in their present home.

The largest number of Rhode Island's elderly live in homes they own. The state's population includes 67,584 elderly homeowners, and 43,609 elderly tenants in rental housing. Of those who rent, approximately 21,000 live in units subsidized by the government.

Six hundred and twenty-eight Rhode Islanders live in 32 licensed sheltered care homes which serve from 8 to 59 residents. Recent changes in admissions requirements for nursing homes will result in more elderly choosing sheltered care in the future.

On a given day, nursing home care for approximately 10,000 people in Rhode Island. For some, the nursing home is a permanent residence. For many others, it is a temporary home during rehabilitation after a stroke or broken hip. Others go into nursing homes after being hospitalized for a serious illness and stay until they die.

Approximately 373 elderly people live in the state long-term care hospitals.

In Rhode Island, a very small number of the elderly live in continuing-care retirement communities and assisted-living complexes. These institutions have become available in Rhode Island only recently, although they have existed in neighboring states for several years. They are often expensive, both in monthly rent and "buy-in fees," which can run as high as $200,000. Only a small portion of elderly Rhode Islanders can afford this option.

In future issues of this *Journal*, Aging 2000's staff will present an analysis of some of the most pressing problems facing the health care of the elderly in Rhode Island and propose solutions to these problems.

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[9] National Council on Patient Information and Education, Priorities and Approaches for Improving Prescription Use by Older Americans (Washington, DC 1987) p. 3.

[10] Blue Cross/Blue Shield of Rhode Island, 1991.

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Director of Health

Rise in 1989 Occurrence Infant Mortality for Rhode Island

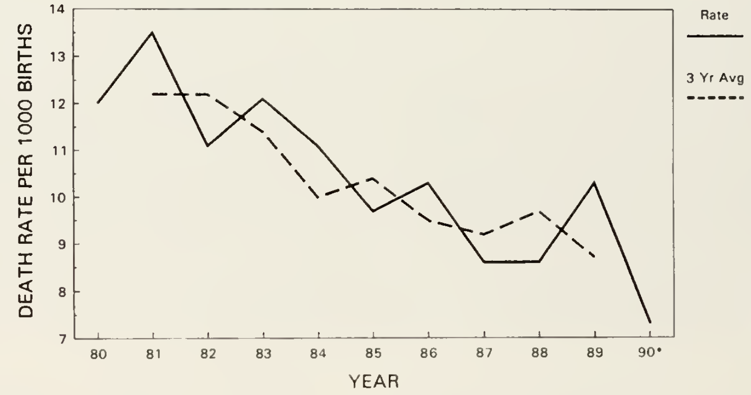
Infant mortality is an important public health status of a population. In 1989, the infant mortality rate among births occurring in Rhode Island rose from 8.6 to 10.3 deaths per 1000 live births (Figure 1). Rhode Island was the only New England state that experienced an increase during this time period.

Figure 1 shows the year to year fluctuation of the infant mortality rate from 1980-90. Even though the three year average rate shows a steady decline it was deemed important to see if the 1989 peak could be explained by underlying trends.

in order to see if there was some identifiable risk factor for this rise, four variables from the death certificate were selected to look at significant trends. These included infant age at death, race, socioeconomic status (attributed from census tract of residence), and state of residence. Data were aggregated into three-year categories (ie, 1984-86 and 1987-89) to increase the power of the analysis.

Table 1 shows that there is virtually no change in age and race patterns between deaths occurring in the two periods investigated. However, there is a significant difference (p = .10) in the socioeconomic status of the infants who died in the two

Figure 1. Occurrence Infant Mortality Rhode Island, 1980-1990



	80	81	82	83	84	85	86	87	88	89	90*
Rate	12	13.5	11.1	12.1	11.1	9.7	10.3	8.6	8.6	10.3	7.3
3 Yr Avg		12.2	12.2	11.4	10	10.4	9.5	9.2	9.7	8.7	

* 1990 Preliminary

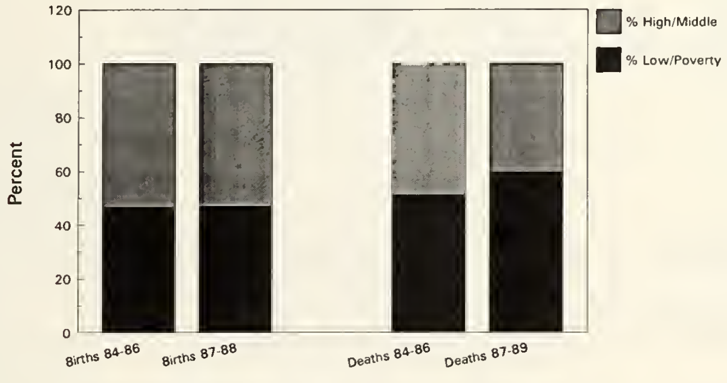
Table 1. Changes in Risk Factor Distribution 1984-86 and 1987-89

YEAR **# Infant Deaths**	**1984-1986** **(n=425)** %	**1987-1989** **(n=411)** %	**Significance**
Age at Death			
< 1 day	48.7	44.3	
1-27 days	28.0	30.7	
28-365 days	23.3	25.1	NS
Race			
White	87.3	86.4	
Non-white	12.7	13.6	NS
SES*			
High/Middle	48.8	40.4	
Low	21.5	25.4	
Poverty	29.8	34.1	p<0.10

Source: Epidemiology Unit, Division of Family Health
NS=not significant at p<0.10 *=RI resident

Submitted by the Division of Family Health, Jane Griffin, MPH and William H. Hollinshead, MD, MPH. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.*

Figure 2.Birth and Infant Death Distribution by Socioeconomic Status Rhode Island, 1984-86 and 1987-89



Note: RI residents only
1989 births not available

periods. The percent of infants dying from low and poverty census tracts was higher in the later 1980s than the mid 1980s.

As Figure 2 shows, the percent of births in low income and poverty areas remained the same from the 1984-86 period to the 1987-88 period, so the excess infant deaths in the 1987-89 period from low and poverty income areas cannot be attributed to a rise in births among women living in these areas. The rise in deaths during this period may be attributed to increasing health and social problems among low income persons (eg, increasing rates of substance abuse, especially cocaine).

Since the low income and poverty socioeconomic areas of the state are the primary target areas for federal and state prenatal programs it is important for the state to monitor developments in this critical indicator. A preliminary count indicates that the 1990 occurrence infant mortality fell to 7.3, the lowest rate to date. Although this decrease is encouraging news, further information on socioeconomic status is needed to determine whether it represents improvement among all population groups in the state.

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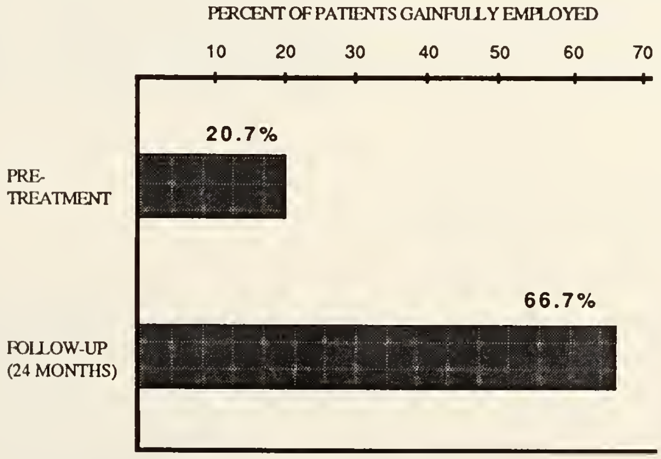

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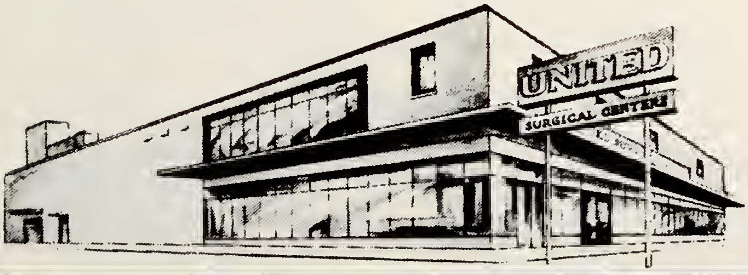

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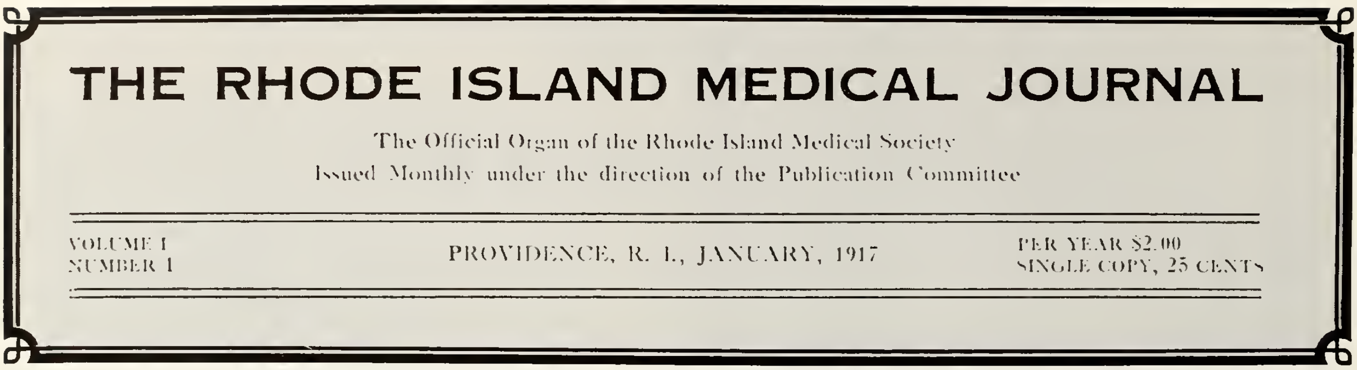

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(October, 1901)

The *Journal* summarizes the events during the annual meeting of the Rhode Island Medical Society, noting the election of eight new members (then called Fellows), including Dr A.H. Miller, later to become editor of the *Journal*. Following the business and scientific meeting, 170 Fellows and invited guests attended the annual dinner. Amongst the after-dinner speakers were: Dr G.F. Keene and President Faunce of Brown University.

The proceedings of the Providence Medical Association are also published. Dr H.B. Potter provides information on recent cases of poisoning by illuminating gas. Therapy " . . . consisted in fresh air and free stimulation with strychnia. Saline infusions were also given."

The leading editorial is entitled, "Public Schools and Public Health." The editorial states, "... if the prevalence of preventable diseases is to be largely diminished during the next score of years, it must be done in a great measure by educating the masses in regard to hygienic and precautionary methods of living. We claim that the public schools should greatly aid in this direction. In them are gathered the children of the working people at an age when they are most susceptible to disease and also to instruction and influence in their way of living so as to best protect themselves from disease in whatever surroundings they may be." The editorial comments on a recent change in the Providence public schools. The common drinking cup has been abolished, and replaced by " . . . the so-called sanitary drinking fountain which has been devised for use in schools and other public places."

A further editorial comments with pride on "Physical Culture in the City Schools." It notes that since 1894, over 400 boys with some crippling physical defects have been placed in special corrective gymnasium classes. "... in the case of girls where no gymnasium has been convenient, the parents have been seen and advised."

The lead article is entitled, "The State Care of Epileptics" and is written by Dr John M. Peters. The author notes, "Of the many classes of patients who seek advice and treatment at the various departments of a hospital there is no more pitiable one than that suffering from epilepsy in its various forms." The article advocates the establishment of congregate colonies where the epileptics may pursue separate but productive lives. He concludes: "Now according to the average given by experts on this subject, there are about 860 epileptics in this state; about 80 of whom are in the State Insane Hospital and State Almshouse; the rest are cared for as best they can be at county poor houses and at home, a burden to themselves, their relatives and the community. How much better it would be in every way if these unfortunates could be looked after by proper medical men, so classified and grouped that the best results of treatment might be secured? They would be at least partially self-supporting, and as a matter of economy it would be advisable to consider the matter. In our small State, with the population centralized, a comparatively small number of buildings in the neighborhood of the State Institutions and under the control of the State Board of Charities and Corrections and the direction of the Superintendent of the State Insane Hospital, and with grounds large enough to allow the inmates to be employed out of doors in pleasant weather, would answer every purpose."

Fifty Years Ago
(October, 1941)

The lead article written by W. Pickles, MD, is entitled, "Meditationes Medicorum" and is a reflection upon certain prominent medical texts of historic importance, particularly Brown's Religio Medici, Paget's Confession Medici, and Cushing's Consecration Medici. (The author, in passing, mentions that Thomas Browne was attending Pembroke College, Oxford, at the same time that Roger Williams was attending Pembroke College, Cambridge.) After reviewing and occasionally quoting from the great collections of medical essays and personal reflections, he closes with this statement: Here then, we have three books, written at widely separated periods of time, by medical men whose training and practice differ as widely; yet through all of them we see an underlying singleness of devotion to medicine and service to mankind. Indeed we may suppose that all three gained common inspiration from the Father of Medicine; at any rate their real philosophy is admirably stated in the old phrase of Hippocrates, "Wherever the art of medicine is loved, there also is love of humanity."

Sir Thomas Browne

A paper on intercapillary glomerular sclerosis is offered by B.E. Clarke, MD. The author notes the initial 1936 paper by Kimmelstiel and Wilson describing glomerular changes in 8 patients with diabetes mellitus of long standing and a nephrotic syndrome (ie, hypertension, albuminuria and edema). Sixty-eight additional cases had been reported in the medical literature and summarized in the paper. The author describes two new cases studied at autopsy at the Rhode Island Hospital, and concludes that the renal lesions of hyaline thickening of the intercapillary glomerular membrane are found only in diabetics and are associated with a syndrome consisting of albuminuria, nephrotic edema, hypertension, low fixed specific gravity of urine, nitrogen retention, and hypo-albuminemia.

The lead editorial comments on the diabetic mortality in Rhode Island, stating, "In recent years Rhode Island has shown the highest death rate from both cancer and diabetes of any state in the union." The editorial observes that this is not necessarily a basis for deep concern. "It must be admitted that the better the preventive medicine in any community and the more excellent the diagnosis and treatment of disease in general, the higher on the mortality lists will go the figures representing the diseases of old age, including degenerative conditions of the cardio-vascular, renal and central nervous systems. Parallel with these must go the records of death from cancer and diabetes, conditions which appear more and more frequently in the later decades of life."

Another editorial summarizes newer treatments for infantile diarrhea. The older methods consisted essentially of one of two approaches: The starvation method, confining intake to water and carbohydrate solutions. This diminished the likelihood of dehydration but furthered the risk of malnutrition; the alternative method, based on the notion that carbohydrates prolonged diarrhea, advocated a protein milk diet. There are recent proponents of the use of raw apple and weak tea, some believing that it is the pectin and cellulose, others thinking that it is the tannic acid which serves to reduce the diarrhea. More recently, a mixture of pectin, agar and dextri-maltose has proven to be more successful. Some claim that pectin " . . . is bacteriocidal, that its constituent galacturonic acid functions as a detoxifying agent, that it absorbs toxins and enmeshes bacteria, that its hydrophilic nature prevents dehydration, and that it is soothing to an inflamed gastrointestinal tract."

Numerous newly published medical textbooks are reviewed. Prices range from a low of $1.50 to a high of $6.00.

Twenty-Five Years Ago
(October, 1966)

The lead article discusses an evaluation of the management of breast carcinoma in the aged female and is written by B.M Webber, MD and M.P. Colbert, MD. The paper summarizes the experience with 29 women with breast cancer all older than 75 years. In the experience of the authors only surgical therapy offers a reasonable degree of cancer control regardless of the presence or absence of other disease. No apparent benefit was achieved in those patients also treated with stilbestrol. Breast cancer in this age group, say the authors, appears to run a course not unlike that in younger patients and if not treated, shortens life.

F. Ronchese, MD writes a paper on warts and the capriciousness of response to treatment. The author considers, briefly, the following forms of therapy: physical agents (eg, radiation, electrocoagulation, high temperature, low temperature); local chemicals (eg, procaine, iodobismuth), oral chemicals (eg, bismuth, methionine, calcium, arsenic), local applications (eg, thymol, benzoic acid, podophyllin, nitric acid), and psychiatric therapies. The author concludes: "The long list of therapeutic procedures suggested or the treatment of warts over the years demonstrates that some of them, particularly the plantar and periungual ones, are most capricious in their response.

They often represent a serious problem. They may be disabling. They are not to be dismissed as something unimportant."

A paper entitled, "Birth Order of Twins, Apgar Score, and Perinatal Mortality" is written by FE Yazbak, MD and R.H. Holden, EdD. Using data from the National Institute for Neurological Diseases and Blindness, the authors analyze 226 twin pairs. They conclude, "The results tend to confirm those previous studies which suggest a higher mortality for the second twin, both for stillbirths and neonatal deaths in the first twenty-four hours. They also strongly indicate that the first twin of a pair is more likely to obtain a higher Apgar score than the second twin. The causes and effects of this advantage remain to be investigated.

S.Y. Deshpande, MD writes on the usefulness of external cardiac massage and defibrillation in the successful treatment of ventricular fibrillation complicating acute myocardial infarction.

JE Mohrnheim, MD and A.C. Butler, MA present a paper supporting the thesis that day care programs are both feasible and effective in the management of a wide range of mental disorders.

M. Tami, MD presents a case of cryptococcal meningitis in a 75-year-old female, the diagnosis verified at autopsy.

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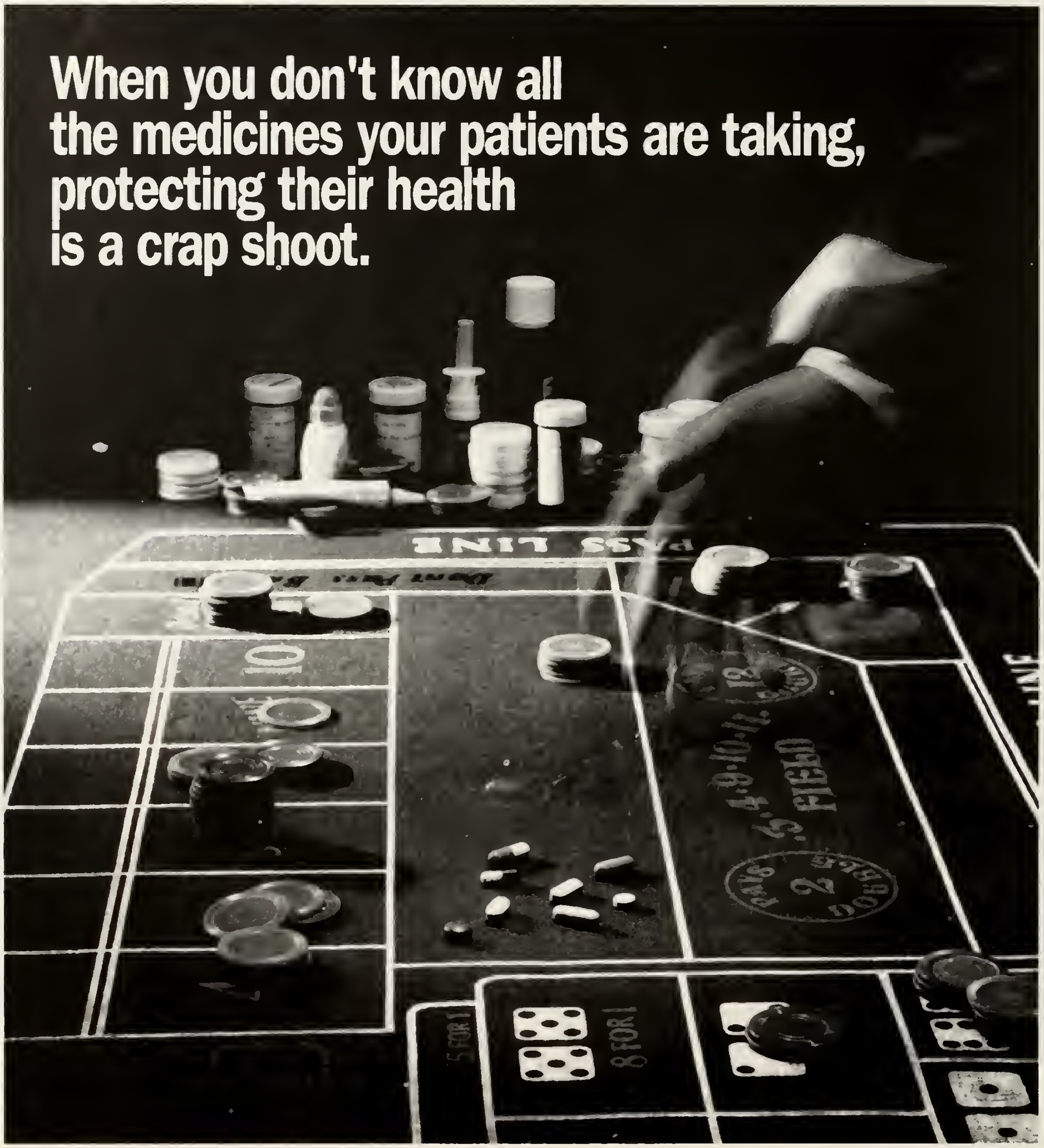
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